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	Patents ADP number *(if you know it)*		
	If the applicant is a corporate body, give the country/state of its incorporation	**BELGIUM** 07346661001.	
4.	Title of the invention	**MOOD DISORDER GENE**	
5.	Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	**BOULT WADE TENNANT 27 FURNIVAL STREET LONDON EC4A 1PQ** **42001** ✓	

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MOOD DISORDER GENE

The invention is concerned with the determination of genetic factors associated with psychiatric health with particular reference to a human gene or genes which contributes to or is responsible for the manifestation of a mood disorder or related disorder in affected individuals and their families. In particular, although not exclusively, the invention provides a method of identifying and characterising such a gene or genes from human chromosome 18 as well as a gene so identified and its expression products. By mood disorders or related disorders is meant the following disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders, version 4 (DSM-IV) taxonomy (DSM-IV codes in parenthesis):- mood disorders (296.XX, 300.4,311,301.13,295.70), schizophrenia and related disorders (295.XX,297.1,298.8,297.3,298.9), anxiety disorders (300.XX,309.81,308.3), adjustment disorders (309.XX) and personality disorders (codes 301.XX).

The methods of the invention are particularly exemplified in relation to genetic factors associated with a family of mood disorders known as Bipolar (BP) spectrum disorders.

Bipolar disorder (BP) is a severe psychiatric condition that is characterized by disturbances in mood, ranging from an extreme state of elation (mania) to a severe state of dysphoria (depression). Two types of bipolar illness have been described: type I BP illness (BPI) is characterized by major depressive episodes alternated with phases of mania, and type II BP illness (BPII), characterized by major depressive episodes alternating with phases of hypomania. Relatives of BP probands have an increased risk for

BP, unipolar disorder (patients only experiencing depressive episodes; UP), cyclothymia (minor depression and hypomania episodes; CY) as well as for schizoaffective disorders of the manic (SAm) and depressive (SAd) type. Based on these observations BP, CY, UP and SA are classified as BP spectrum disorders. The involvement of genetic factors in the etiology of BP spectrum disorders was suggested by family, twin and adoption studies (Tsuang and Faraone (1990), The Genetics of Mood Disorders, Baltimore, The John Hopkins University Press). However, the exact pattern of transmission is unknown. In some studies, complex segregation analysis supports the existence of a single major locus for BP (Spence et al. (1995), Am J. Med. Genet (Neuropsych. Genet.) 60 pp 370-376). Other researchers propose a liability-threshold-model, in which the liability to develop the disorder results from the additive combination of multiple genetic and environmental effects (McGuffin et al. (1994), Affective Disorders; Seminars in Psychiatric Genetics Gaskell, London pp 110-127).

Due to the complex mode of inheritance, parametric and nonparametric linkage strategies are applied in families in which BP disorder appears to be transmitted in a Mendelian fashion. Early linkage findings on chromosomes 11p15 (Egeland et al. (1987), Nature 325 pp 783-787) and Xq27-q28 (Mendlewicz et al. (1987) The Lancet 1 pp 1230 -1232; Baron et al. (1987) Nature 326 pp 289-292) have been controversial and could initially not be replicated (Kelsoe et al. (1989) Nature 242 pp 238-243; Baron et al. (1993) Nature Genet 3 pp 49-55). With the development of a human genetic map saturated with highly polymorphic markers and the continuous development of data analysis techniques, numerous new linkage searches

were started. In several studies, evidence or suggestive evidence for linkage to particular regions on chromosomes 4, 12, 18, 21 and X was found (Blackwood et al. (1996) Nature Genetics 12 pp 427-430, Craddock et al. (1994) Brit J. Psychiatry 164 pp 355-358, Berrettini et al. (1994), Proc Natl Acad Sci USA 91 pp 5918-5921, Straub et al. (1994) Nature Genetics 8 pp 291-296 and Pekkarinen et al. (1995) Genome Research 5 pp 105-115). In order to test the validity of the reported linkage results, these findings have to be replicated in other, independent studies.

Recently, linkage of bipolar disorder to the pericentromeric region on chromosome 18 was reported (Berrettini et al. 1994). Also a ring chromosome 18 with break-points and deleted regions at 18pter-p11 and 18q23-qter was reported in three unrelated patients with BP illness or relates syndromes (Craddock et al. 1994). The chromosome 18p linkage was replicated by Stine et al. (1995) Am J. Hum Genet 57 pp 1384-1394, who also reported suggestive evidence for a locus on 18q21.2-q21.32 in the same study. Interestingly, Stine et al. observed a parent-of-origin effect: the evidence of linkage was the strongest in the paternal pedigrees, in which the proband's father or one of the proband's father's sibs is affected.

In an independent replication study, the present inventors tested linkage with chromosome 18 markers in 10 Belgian families with a bipolar proband. To localize causative genes the linkage analysis or likelihood method was used in these families. This method studies within a family the segregation of a defined disease phenotype with that of polymorphic genetic markers distributed in the human genome. The

likelihood ratio of observing cosegregation of the disease and a genetic marker under linkage versus no linkage is calculated and the log of this ratio or the log of the odds is the LOD score statistic z. A LOD score of 3 (or likelihood ratio of 1000 or greater) is taken as significant statistical evidence for linkage. In the inventors' study no evidence for linkage to the pericentromeric regions was found, but in one of the families, MAD31, a Belgian family of a BPII proband, suggestive linkage was found with markers located at 18q21.33-q23 (De bruyn et al. (1996) Biol Psychiatry 39 pp 679-688). Multipoint linkage analysis gave the highest LOD score in the interval between STR (Short Tandem Repeats) polymorphisms D18S51 and D18S61, with a maximum multipoint LOD score of +1.34. Simulation studies indicated that this LOD score is within the range of what can be expected for a linked marker given the information available in the family. Likewise, an affected sib-pair analysis also rejected the null-hypothesis of nonlinkage for several of the markers tested. Two other groups also found evidence for linkage of bipolar disorder to 18q (Freimer et al. (1996) Nature Genetics 12 pp 436-441, Coon et al. (1996) Biol Psychiatry 39 pp 689 to 696). Although the candidate regions in the different studies do not entirely overlap, they all suggest the presence of a susceptibility locus at 18q21-q23.

The inventors have now carried out further investigations into the 18q chromosomal region in family MAD31. By analysis of cosegregation of bipolar disease in MAD31 with twelve STR polymorphic markers previously located between the aforementioned markers D18S51 and D18S61 and subsequent LOD score analysis as described above, the inventors have further refined the candidate region of chromosome 18 in which a gene

associated with mood disorders such as bipolar spectrum disorders may be located and have constructed a physical map. The region in question when removed from the totality of the human genome may thus be used to locate, isolate and sequence a gene or genes which influences psychiatric health and mood.

The inventors have also constructed a YAC (yeast artificial chromosome) contig map of the candidate region to determine the relative order of the twelve STR markers mapped by the cosegregational analysis and they have identified seven clones from the YAC library incorporating the candidate region. Standard procedures well-known to one skilled in the art are applied to the identified YAC clones and, where applicable, to the DNA from an individual afflicted with a mood disorder as defined herein, in the process of identifying and characterising the relevant gene or genes. For example, the inventors are able to make use of the previously identified apparent association between trinucleotide repeat expansions (TRE) within the human genome and the phenomenon of anticipation in mood disorders (Lindblad et al. (1995), Neurobiology of Disease 2 pp 55-62 and O'Donovan et al. (1995), Nature Genetics 10 pp 380-381) to screen for TRE's in the selected YAC clones in order to identify candidate genes in the region of interest on human chromosome 18. A variety of other known procedures can also be applied to the said YAC clones to identify candidate genes as discussed below.

Accordingly, in a first aspect the present invention comprises the use of an 8.9 cM region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979 or a fragment thereof for identifying at least one human gene, including mutated and polymorphic variants thereof, which is associated

with mood disorders or related disorders as defined above. As will be described below, the present inventors have identified this candidate region of chromosome 18q for such a gene, by analysis of cosegregation of bipolar disease in family MAD31 with 12 STR polymorphic markers previously located between D18S51 and D18S61 and subsequent LOD score analysis.

In a second aspect the invention comprises the use of a YAC clone comprising a portion of human chromosome 18q disposed between polymorphic markers D18S60 and D18S61 for identifying at least one human gene, including mutated or polymorphic variants thereof, which is associated with mood disorders or related disorders as defined above. D18S60 is close to D18S51 so the particular YAC clones for use are those which have an artificial chromosome spanning the candidate region of human chromosome 18q between polymorphic markers D18S51 and D18S61 as identified by the present inventors in their earlier paper (De bruyn et al. (1996)).

Particular YACs covering the candidate region which may be used in accordance with the present invention are 961_h_9, 942_c_3, 766_f_12, 731_c_7, 907_e_1, 752-g-8 and 717_d_3, preferred ones being 961_h_9, 766_f_12 and 907_e_1 since these have the minimum tiling path across the candidate region. Suitable YAC clones for use are those having an artificial chromosome spanning the refined candidate region between D18S68 and D18S979.

There are a number of methods which can be applied to the candidate regions of chromosome 18q as defined above, whether or not present in a YAC, to identify a candidate gene or genes associated with mood disorders or related disorders. For example, as aforesaid, there is an apparent association between

the extent of trinucleotide repeat expansions (TRE) in the human genome and the presence of mood disorders. Accordingly, in a third aspect the present invention comprises a method of identifying at least one human gene, including mutated and polymorphic variants thereof, which is associated with a mood disorder or related disorder as defined herein which comprises detecting nucleotide triplet repeats in the region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979.

An alternative method of identifying said gene or genes comprises fragmenting a YAC clone comprising a portion of human chromosome 18q disposed between polymorphic markers D18S60 and D18S61, for example one or more of the seven aforementioned YAC clones, and detecting any nucleotide triplet repeats in said fragments, in particular repeats of CAG or CTG. Nucleic acid probes comprising at least 5 and preferably at least 10 CTG and/or CAG triplet repeats are a suitable means of detection when appropriately labelled. Trinucleotide repeats may also be determined using the known RED (repeat expansion detection) system (Shalling et al.(1993), Nature Genetics 4 pp 135-139).

In a fourth embodiment the invention comprises a method of identifying at least one gene, including mutated and polymorphic variants thereof, which is associated with a mood disorder or related disorder and which is present in a YAC clone spanning the region of human chromosome 18q between polymorphic markers D18S60 and D18S61, the method comprising the step of detecting the expression product of a gene incorporating nucleotide triplet repeats by use of an antibody capable of recognising a protein with an amino acid sequence comprising a string of at least 8,

but preferably at least 12, continuous glutamine residues. Such a method may be implemented by subcloning YAC DNA, for example from the seven aforementioned YAC clones, into a human DNA expression library. A preferred means of detecting the relevant expression product is by use of a monoclonal antibody, in particular mAB1C2, the preparation and properties of which are described in International Patent Application Publication No WO 97/17445.

Further embodiments of the present invention relate to methods of identifying the relevant gene or genes which involve the sub-cloning of YAC DNA as defined above into vectors such as BAC (bacterial artificial chromosome) or PAC (P1 or phage artificial chromosome) or cosmid vectors such as exon-trap cosmid vectors. The starting point for such methods is the construction of a contig map of the region of human chromosome 18q between polymorphic markers D18S60 and D18S61. To this end the present inventors have sequenced the end regions of the fragment of human DNA in each of the seven aforementioned YAC clones and these sequences are disclosed herein. Following subcloning of YAC DNA into other vectors as described above, probes comprising these end sequences or portions thereof, in particular those sequences shown in Figures 1 to 11 herein, together with any known sequenced tagged site (STS) in this region, as described in the YAC clone contig shown herein, as can be used to detect overlaps between said subclones and a contig map can be constructed. Also the known sequences in the current YAC contig can be used for the generation of contig map subclones.

One route by which a gene or genes which is associated with a mood disorder or associated disorder

can be identified is by use of the known technique of exon trapping.

This is an artificial RNA splicing assay, most often making use in current protocols of a specialized exon-trap cosmid vector. The vector contains an artificial minigene consisting of a segment of the SV40 genome containing an origin of replication and a powerful promoter sequence, two splicing-competent exons separated by an intron which contains a multiple cloning site and an SV40 polyadenylation site.

The YAC DNA is subcloned in the exon-trap vector and the recombinant DNA is transfected into a strain of mammalian cells. Transcription from the SV40 promoter results in an RNA transcript which normally splices to include the two exons of the minigene. If the cloned DNA itself contains a functional exon, it can be spliced to the exons present in the vector's minigene. Using reverse transcriptase a cDNA copy can be made and using specific PCR primers, splicing events involving exons of the insert DNA can be identified. Such a procedure can identify coding regions in the YAC DNA which can be compared to the equivalent regions of DNA from a person afflicted with a mood disorder or related disorder to identify the relevant gene.

Accordingly, in a fifth aspect the invention comprises a method of identifying at least one human gene, including mutated variants and polymorphisms thereof, which is associated with a mood disorder or related disorder which comprises the steps of:

(1) transfecting mammalian cells with exon trap cosmid vectors prepared and mapped as described above;

(2) culturing said mammalian cells in an

appropriate medium;

(3) isolating RNA transcripts expressed from the SV40 promoter;

(4) preparing cDNA from said RNA transcripts;

(5) identifying splicing events involving exons of the DNA subcloned into said exon trap cosmid vectors to elucidate positions of coding regions in said subcloned DNA;

(6) detecting differences between said coding regions and equivalent regions in the DNA of an individual afflicted with said mood disorder or related disorder; and

(7) identifying said gene or mutated or polymorphic variant thereof which is associated with said mood disorder or related disorders.

As an alternative to exon trapping the YAC DNA may be subcloned into BAC, PAC, cosmid or other vectors and a contig map constructed as described above. There are a variety of known methods available by which the position of relevant genes on the subcloned DNA can be established as follows:

(a) cDNA selection or capture (also called direct selection and cDNA selection): this method involves the forming of genomic DNA/cDNA heteroduplexes by hybridizing a cloned DNA (e.g. an insert of a YAC DNA), to a complex mixture of cDNAs, such as the

inserts of all cDNA clones from a specific (e.g. brain) cDNA library. Related sequences will hybridize and can be enriched in subsequent steps using biotin-streptavidine capturing and PCR (or related techniques);

(b) hybridization to mRNA/cDNA: a genomic clone (e.g. the insert of a specific cosmid) can be hybridized to a Northern blot of mRNA from a panel of culture cell lines or against appropriate (e.g. brain) cDNA libraries. A positive signal can indicate the presence of a gene within the cloned fragment;

(c) CpG island identification: CpG or HTF islands are short (about 1 kb) hypomethylated GC-rich (> 60%) sequences which are often found at the 5′ ends of genes. CpG islands often have restriction sites for several rare-cutter restriction enzymes. Clustering of rare-cutter restriction sites is indicative of a CpG island and therefore of a possible gene. CpG islands can be detected by hybridization of a DNA clone to Southern blots of genomic DNA digested with rare-cutting enzymes, or by island-rescue PCR (isolation of CpG islands from YACs by amplifying sequences between islands and neighbouring *Alu*-repeats);

(d) zoo-blotting: hybridizing a DNA clone (e.g. the insert of a specific cosmid) at reduced

stringency against a Southern blot of genomic DNA samples from a variety of animal species. Detection of hybridization signals can suggest conserved sequences, indicating a possible gene.

Accordingly, in a sixth aspect the invention comprises a method of identifying at least one human gene including mutated and polymorphic variants thereof which is associated with a mood disorder or related disorder which comprises the steps of:

(1) subcloning the YAC DNA as described above into a cosmid, BAC, PAC or other vector;

(2) using the nucleotide sequences shown in any one of Figures 1 to 11 or any other sequenced tagged site (STS) in this region as in the YAC clone contig described herein, or part thereof consisting of not less than 14 contiguous bases or the complement thereof, to detect overlaps amongst the subclones and construct a map thereof;

(3) identifying the position of genes within the subcloned DNA by one or more of CpG island identification, zoo-blotting, hybridization of the subcloned DNA to a cDNA library or a Northern blot of mRNA from a panel of culture cell lines;

(4) detecting differences between said genes and equivalent region of the DNA of an individual afflicted with a mood disorder or related disorder; and

(5) identifying said gene which is associated with said mood disorders or related disorders.

If the cloned YAC DNA is sequenced, computer analysis can be used to establish the presence of relevant genes. Techniques such as homology searching and exon prediction may be applied.

Once a candidate gene has been isolated in accordance with the methods of the invention more detailed comparisons may be made between the gene from a normal individual and one afflicted with a mood disorder such as a bipolar spectrum disorder. For example, there are two methods, described as "mutation testing", by which a mutation or polymorphism in a DNA sequence can be identified. In the first the DNA sample may be tested for the presence or absence of one specific mutation but this requires knowledge of what the mutation might be. In the second a sample of DNA is screened for any deviation from a standard (normal) DNA. This latter method is more useful for identifying candidate genes where a mutation is not identified in advance.

In addition the following techniques may be further applied to a gene identified by the above-described methods to identify differences between genes from normal or healthy individuals and those afflicted with a mood disorder or related disorder:

(a) Southern blotting techniques: a clone is hybridized to nylon membranes containing genomic DNA digested with different restriction enzymes of patients and healthy individuals. Large differences between patients and healthy individuals can be

visualized using a radioactive labelling protocol;

(b) heteroduplex mobility in polyacrylamide gels: this technique is based on the fact that the mobility of heteroduplexes in non-denaturing polyacrylamide gels is less than the mobility of homoduplexes. It is most effective for fragments under 200 bp;

(c) single-strand conformational polymorphism analysis (SSCP or SSCA): single stranded DNA folds up to form complex structures that are stabilized by weak intramolecular bonds. The electrophoretic mobilities of these structures on non-denaturing polyacrylamide gels depends on their chain lengths and on their conformation;

(d) chemical cleavage of mismatches (CCM): a radiolabelled probe is hybridized to the test DNA, and mismatches detected by a series of chemical reactions that cleave one strand of the DNA at the site of the mismatch. This is a very sensitive method and can be applied to kilobase-length samples;

(e) enzymatic cleavage of mismatches: the assay is similar to CCM, but the cleavage is performed by certain bacteriophage enzymes.

(f) denaturing gradient gel electrophoresis: in this technique, DNA duplexes are forced to migrate through an electrophoretic gel in

which there is a gradient of increasing amounts of a denaturant (chemical or temperature). Migration continues until the DNA duplexes reach a position on the gel wherein the strands melt and separate, after which the denatured DNA does not migrate much further. A single base pair difference between a normal and a mutant DNA duplex is sufficient to cause them to migrate to different positions in the gel;

(g) direct DNA sequencing.

It will be appreciated that with respect to the methods described herein, in the step of detecting differences between coding regions from the YAC and the DNA of an individual afflicted with a mood disorder or related disorder, the said individual may be anybody with the disorder and not necessary a member of family MAD31.

In accordance with further aspects the present invention provides an isolated human gene and variants thereof associated with a mood disorder or related disorder and which is obtainable by any of the above described methods, an isolated human protein encoded by said gene and a cDNA encoding said protein.

In the experimental report which follows reference will be made to the following figures:

FIGURE 1 shows a sequence of nucleotides which is the left arm end-sequence of YAC 766_f_12;

FIGURE 2 shows a sequence of nucleotides which is a right arm end-sequence of YAC 766_f_12;

FIGURE 3 shows a sequence of nucleotides which is a left arm end-sequence of YAC 717_d_3;

FIGURE 4 shows a sequence of nucleotides which is a right arm end-sequence of YAC 717_d_3;

FIGURE 5 shows a sequence of nucleotides which is a right arm end-sequence of YAC 731_c_7;

FIGURE 6 shows a sequence of nucleotides which is a left arm end-sequence of YAC 752_g_8;

FIGURE 7 shows a sequence of nucleotides which is a left arm end-sequence of YAC 942_c_3;

FIGURE 8 shows a sequence of nucleotides which is a right arm end-sequence of YAC 942_c_3;

FIGURE 9 shows a sequence of nucleotides which is a left arm end-sequence of YAC 961_h_9;

FIGURE 10 shows a sequence of nucleotides which is a right arm end-sequence of YAC 961_h_9;

FIGURE 11 shows a sequence of nucleotides which is a left arm end-sequence of YAC 907_e_1;

FIGURE 12 shows a pedigree of family MAD31;

FIGURE 13 shows the haplotype analysis for family MAD13. Affected individuals are represented by filled diamonds, open diamonds represent individuals who were asymptomatic at the last psychiatric evaluation. Dark gray bars represent markers for which it cannot be deduced if they are recombinant; and

FIGURE 14 shows the YAC contig map of the region of human chromosome 18 between the polymorphic markers D18560 and D18561. Black lines represent positive hits. YACs are not drawn to scale.

Experimental

(a) Family Data

Clinical diagnoses in MAD31, a Belgian family with a BPII proband were described in detail in De bruyn et al 1996. In that study only the 15 family members who were informative for linkage analysis were selected for additional genotypings. The different clinical diagnoses in the family were as follows:
1 BPI, 2 BPII, 2UP, 4 Major depressive disorder (MDD), 1 SAm and 1 SAd.
The pedigree of the MAD31 family is shown in Figure 12.

(b) Genotyping of Family Members

All short tandem repeat (STR) genetic markers are di- or tetranucleotide repeat polymorphisms. Information concerning the genetic markers used in this study was obtained from several sources on the internet: Genome DataBase (GDB, http://gdbwww.gdb.org/), GenBank (http://www.ncbi.nlm.nih.gov/), Cooperative Human Linkage Center (CHLC, http://www.chlc.org/), Eccles Institute of Human Genetics (EIHG, http://www.genetics.utah.edu/) and Généthon (http://www.genethon.fr/). Standard PCR was performed in a 25 μl volume containing 100 ng genomic DNA, 200 mM of each dNTP, 1.25 mM $MgCl_2$, 30 pmol of each primer and 0.2 units Goldstar DNA polymerase

(Eurogentec). One primer was end-labelled before PCR with [gamma-^{32}P]ATP and T4 polynucleotide kinase. After an initial denaturation step at 94°C for 2 min, 27 cycles were performed at 94°C for 1 min, at the appropriate annealing temperature for 1.5 min and extension at 72°C for 2 min. Finally, an additional elongation step was performed at 72°C for 5 min. PCR products were detected by electrophoresis on a 6% denaturing polyacrylamide gel and by exposure to an X-ray sensitive film. Successfully analysed STSs, STRs and ESTs covering the refined candidate region are fully described herein on pages 29 to 47.

(c) Lod score analysis.

Two-point lod scores were calculated for 3 different disease models using Fastlink 2.2. (Cottingham et al. 1993). For all models, a disease gene frequency of 1% and a phenocopy rate of 1/1000 was used. Model 1 included all patients and unaffected individuals with the latter individuals being assigned to a disease penetrance class depending on their age at examination. The 9 age-dependent penetrance classes as described by De bruyn et al (1996) were multiplied by a factor 0.7 corresponding to a reduction of the maximal penetrance of 99% to 70% for individuals older than 60 years (Ott 1991). Model 2 is similar to model 1, but patients were assigned a diagnostic stability score, calculated based on clinical data such as the number of episodes, the number of symptoms during the worst episode and history of treatment (Rice et al. 1987, De bruyn et al. 1996). Model 3 is as model 1 but includes only patients.

(d) Construction of the YAC contig - protocols

Growing of YACs and extraction of YAC DNA was done according to standard protocols (Silverman, 1995). For the construction of the YAC-contig spanning the chromosome 18q candidate region, the data of the physical map based on sequence tagged sites (STSs) (Hudson et al. 1995) was consulted on the Whitehead Institute (WI) Internet site (http://www-genome.wi.mit.edu/). CEPH mega-YACs were obtained from the YAC Screening Centre Leiden (YSCL, the Netherlands) and from CEPH (Paris, France). The YACs were analyzed for the presence of STSs and STRs, previously located between D18S51 and D18S61, by touchdown PCR amplification. Information on the STSs/STRs was obtained from the WI, GDB, Généthon, CHLC and GenBank sites on the Internet. Thirty PCR cycles consisted of: denaturation at 94°C for 1 min, annealing (2 cycles for each temperature) starting from 65°C and decreasing to 51°C for 1.5 min and extension at 72°C for 2 min. This was followed by 10 cycles of denaturation at 94°C for 1 min, annealing at 50°C for 1.5 min and extension at 72°C for 2 min. A final extension step was performed for 10 min at 72°C. Amplified products were visualised by electrophoresis on a 1% TBE agarose gel and ethidium bromide staining.

(e) Ordering of the STR markers.

Twelve STR markers, previously located between D18S51 and D18S61, were tested for cosegregation with bipolar disease in family MAD31. The parental haplotypes were reconstructed from genotype information of the siblings in family MAD31 and minimalizing the number of possible recombinants. The

result of this analysis is shown in Figure 13. The father was not informative for 3 markers, the mother was not informative for 5 markers. Haplotypes in family MAD31 suggested the following order for the STR markers analysed: cen-[S51-S68-S346]-[S55-S969-S1113-S483-S465]-[S876-S477]-S979-[S466-S817-S61]-tel. The order relative to each other of the markers between brackets could not be inferred from our haplotype data. The marker order in family MAD31 was compared with the marker order obtained using different mapping techniques and the results shown in Table 1 below.

Table 1. Comparison of the order of the markers within the 18q candidate region for bipolar disorder, among several maps.

Marker*	Genetic maps		Radiation hybrid map
	Généthon	Marshfield	(Giacalone et al. 1996)
D18S51		(-)3.4cM	(-)27.9 cR
D18S68	0 cM	0 cM	0 cR
D18S346		5.3 cM	52.2 cR
D18S55	0.1 cM	0 cM	72.5 cR
D18S969		0.6 cM	
D18S1113	0.7 cM		
D18S483	2.5 cM	3.2 cM	88 cR
D18S465	4.5 cM	5.3 cM	101.3 cR
D18S876			
D18S477	4.4 cM	5.3 cM	166.4 cR
D18S979		8.9 cM	
D18S466	7.6 cM	11.1 cM	212.4 cR
D18S61	8.4 cM	11.8 cM	249.5 cR
D18S817		5.3 cM	260.6 cR

* Order according to haplotyping results in family MAD31.

(-) Marker is located proximal of D18S68.

D18S68, common to all 3 maps, was taken as the map anchor point, and the genetic distance in cM or cR of the other markers relative to D18S68 are given. The marker order is in good agreement with the order of the markers on the recently published chromosome 18 radiation hybrid map (Giacalone et al. (1996) Genomics 37:9-18) and the WI YAC-contig map (http://www-genome.wi.mit.edu/). However, a few discrepancies with other maps were observed. The only discrepancy with the Généthon genetic map is the reversed order of D18S465 and D18S477. Two discrepancies were observed with the Marshfield map (http://www.marshmed.org/genetics/). The present inventors mapped D18S346 above D18S55 based on maternal haplotypes, but on the Marshfield maps D18S346 is located between D18S483 and D18S979. The inventors also placed D18S817 below D18S979, but on the Marshfield map this marker is located between D18S465 and D18S477. However, the location of D18S346 and D18S817 is in agreement with the chromosome 18 radiation hybrid map of Giacalone et al. (1996). One discrepancy was also observed with the WI radiation hybrid map (http://www-genome.wi.mit.edu/), in which D18S68 was located below D18S465. However, the inventors as well as other maps placed this marker above D18S55.

(f) Lod score analysis and refinement of the candidate region.

Lod score analysis gave positive results with all markers, confirming the previous observation that 18q21.33-q23 is implicated in BP disease, at least in family MAD31 (De bruyn et al. 1996). Summary statistics of the lod score analysis under all models

are given in table 2 below.

Table 2. Summary statistics of the two-point lod scores in MAD31.

Marker	Model 1			Model 2			Model 3		
	Z at θ=0.0	Zmax	θmax	Z at θ=0.0	Zmax	θmax	Z at θ=0.0	Zmax	θmax
D18S51	-0.19	0.73	0.1	0.94	0.94	0.01	0.08	0.54	0.1
D18S68	-0.19	0.73	0.1	0.94	0.94	0.01	0.07	0.55	0.1
D18S346	-0.19	0.73	0.1	0.94	0.94	0.01	0.07	0.55	0.1
D18969	1.40	1.40	0.0	1.27	1.27	0.0	1.20	1.20	0.0
D18S1113	2.01	2.01	0.0	1.87	1.87	0.0	1.77	1.77	0.0
D18S876	2.01	2.01	0.0	1.87	1.87	0.0	1.77	1.77	0.0
D18S477	2.01	2.01	0.0	1.87	1.87	0.0	1.77	1.77	0.0
D18S979	-0.18	0.77	0.1	1.08	1.08	0.0	0.08	0.54	0.0
D18S817	-0.19	0.73	0.1	1.08	1.08	0.0	0.07	0.55	0.1
D18S61	-0.21	0.73	0.1	1.08	1.08	0.0	0.07	0.54	0.1

D18S55, D18S483, D18S465 and D18S466 were not informative.

The highest two-point lod score (+2.01 at θ=0.0) was obtained with markers D18S1113, D18S876 and D18S477 under model 1 in the absence of recombinants (table 2). In model 1, all indiviuals with a BP spectrum disorder are considered affected and fully contributing to the linkage analysis.
Before the fine mapping the candidate region was flanked by D18S51 and D18S61, which are separated by a genetic distance of 15.2 cM on the Marshfield map or 13.1 cM on the Généthon map. The informative recombinants with D18S51 and D18S61 were observed in 2 affected individuals (II.10 and II.11 in Fig. 13). However, since no other markers were tested within the candidate region it was not known whether these individuals actually shared a region identical-by-descent (IBD). The additional genetic mapping data now indicate that all affected individuals are sharing alleles at D18S969, D18S1113, D18S876 and D18S477 (Fig. 13, boxed haplotype). Also, alleles from markers D18S483 and D18S465 are probably IBD, but these markers were not informative in the affected parent I.1. Obligate recombinants were observed with the STR markers D18S68, D18S346, D18S979 and D18S817 (Table 2, fig. 13) Since discrepancies between different maps were observed for the locations of D18S346 and D18S817, the present inventors used D18S68 and D18S979 to redefine the candidate region for BP disease. The genetic distance between these 2 markers is 8.9 cM based on the Marshfield genetic map (http.//www.marshmed.org/genetics/).

(g) Construction of the YAC contig.

According to the WI integrated map 56 CEPH megaYACs are located in the initial candidate region

contained between D18S51 and D18S61 (Chumakov et al. (1995) Nature 377 Suppl., De bruyn et al. 1996). From these YACs, those were selected that were located in the region between D18S60 and D18S61. D18S51 is not presented on the WI map, but is located close to D18S60 according to the Marshfield genetic map (http.//www.marshmed.org/genetics/). To limit the number of potential chimaeric YACs,YACs were eliminated that were also positive for non-chromosome 18 STSs . As such, 25 YACs were selected (see Figure 14), and placed in a contig based on the technique of YAC contig mapping, i.e. sequences from sequence tagged sites (STSs), simple tandem repeats (STRs) and expressed sequenced tags (ESTs), known to map between D18S60 and D18S61, were amplified by PCR on the DNA from the YAC clones. The STS, STR and EST sequences used, are described from page 29 to 47. Positive YAC clones were assembled in a YAC contig map (Figure 14).

Three gaps remained in the YAC contig, of which one, between D18S876 and GCT3G01, was located in the refined candidate region. To close the gap between D18S876 and GCT3G01, 14 YAC clones (Table 3, on page 54) were further analysed. End fragments from YAC clones 766_f_12 (SV11R), 752_g_8 (SV31L), 942_c_3 (SV10R) were obtained and sequenced (see pages 47-53). Primers from these three sequences were selected, and DNA of each of the 14 YAC clones was amplified by PCR. As indicated in Table 3, overlaps were obtained between 7 YAC clones on the centromeric side, and two YAC clones on the telomeric site 717_d_3 and 907_e_1).

The final YAC contig is shown in Figure 14. In the figure, only the YAC clones which rendered unambiguous hits with the chromosome 18 STSs, STRs and ESTs are shown. In a few cases, weak positive signals were also obtained with some of the YAC clones, which

likely represent false positive results. However, these signals did not influence the alignment of the YAC clones in the contig. Although, all YACs known to map in the region were tested as well as all available STSs/STRs, initially, the gap in the YAC contig was not closed. However, this was subsequently achieved by determining the end-sequences of the eight selected YACs (see below). The order of the markers provided by the YAC contig map is in complete agreement with the marker order provided by the WI map which integrates information from the genetic map, the radiation hybrid map and the STS YAC contig map (Hudson et al. 1995). Also, the YAC contig map confirms the order of the STR markers as suggested by the haplotype analysis in family MAD31. Moreover, the YAC contig map provides additional information on the relative order of the STR markers. For example, D18S55 is present in YAC 931_g_10 but not in 931_f_1 (Fig.14), separating D18S55 from its cluster [S55-S969-S1113-S483-S465] obtained by haplotype analysis in family MAD31. The centromeric location of D18S55 is defined by the STS/STR content of surrounding YACs (Fig. 14). If we combine the haplotype data and the YAC contig map the following order of STR markers is obtained: cen-[S51-S68-S346]-S55-[S969-S1113]-[S483-S465]-S876-S477-S979-S466-[S817-S61]-tel.

Out of the 25 YAC clones spanning the whole contig, seven YAC clones were selected in order to identify the minimal tiling path (Table 4). These 7 YAC clones cover the whole refined chromosome 18 region. Furthermore, YAC clones should preferably be non-chimeric, i.e. they should only contain fragments from human chromosome 18. In order to examine for the presence of chimerism, both ends of these YACs were subcloned and sequenced (pages 48 to 54). For each of

the sequences, primers were obtained, and DNA from a monochromosomal mapping panel was amplified by PCR using these primers. As indicated on pages 48 to 54, some of the YAC clones contained fragments from other chromosomes, apart from human chromosome 18.

Three YAC clones were then selected comprising the minimum tiling path (Table 5). These three YAC clones were stable as determined by pulsed field gel electrophoresis and their seizes correspond well to the published sizes. These YAC clones were transferred to other host yeast strains for restriction mapping, and are the subject to further subcloning.

Description of the succesfully analysed STSs, STRs and ESTs covering the refined candidate region.

Explanations:

- STS: Sequence Tagged Site
- STR: Simple Tandem Repeat
- EST: Expressed Sequence Tag

These markers are ordered from the centromere to the telomere. Only the markers that were effectively tested and that worked on the YACs are given.

List:

1. D18S60:

Database ID: AFM178XE3 (Also known as 178xe3, Z16781, D18S60)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = CCTGGCTCACCTGGCA
Right = TTGTAGCATCGTTGTAATGTTCC
Product Length = 157
Review complete sequence:
AGCTATCCTGGCTCACCTGGCAAAAATACAGTGTATACACACACACACAC
ACACACACACACACACACAGAGTGTNTTANTNATTCCAGCAAATAATATTA
CATATAAAAGATCTAATTGGTTCATCATGTAAATTTAGTAGGAACATTACA
ACGATGCTACAAGANTTTATCCAAAACTGAGATTTCCTTAGAATATCTGTT
AAAAGTAATTTTATTCAGTTAATAGAAATTCTATTGAAAACATCAAACTTAT
AAAGCT

Genbank ID: Z16781
Description: H. sapiens (D18S60) DNA segment containing (CA) repeat; clone
Search for GDB entry

2. WI-9222:

Database ID: UTR-03540 (Also known as G06101, D18S1033, 9222, X63657)
Source: WICGR: Primers derived from Genbank sequences
Chromosome: Chr18

Primers:

Left = GATCCCATAAAGCTACGAGGG
Right = GAGTCTAAAGACAAGAAAGCATTGC
Product Length = 99
Review complete sequence:

TCTTCTTACCCCTTGGAAGAAGACTGTTTCCAAATAATTTGAACAGCTTG
CTGCTAAATGGGACCCAATTTTTGGCCTATAGACACTTATGTATTGTTTTC
GAATACGTCAGATTGGACCAGTGCTCTTCAGGAATGTGGCTGCAAGCAA
GGGGCTAGAAGTTCACCTCCTGACAGTATTATTAATACTATGCAAATATG
GAATAGGAGACCATTTGATTTTCTAGGCTTTGTGGTAGAGAGGTGAAGG
TATGAGAATTAATAGCGTGTGAACAAAGTAAAGAACAGGATTCCAGAATG
ATCATTAAATTTGTTTCTATTTATTCTTTTTTGCCCCCCTAGAGATTAAGTC
CAGAAATGTACTTTCTGGCACATAAAGAAATCTTGAGGACTTTGTTTAAAC
CTTCCATAAAAAAAACAATTTTCGGTTTCTCGGGTNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNT
TCTTTCTTTGTGTATTTTATTCAAGATGAGTTGGACCCATTGCCAGTGAGT
CTGAATGTCACTGACAGCCCTGTGTTGTGCTCAGGACTCACTCTGCTGC
TGGTGGAAACTCATGGCTTCTCTCTCTCTTTGATCCCATAAAGCTACGAG
GGGGACGGGAGAGGGCAGTGCAATGGGAAGTAAAGAGATATTTTCCAG
TAGGAAAAGCAATGCTTTCTTGTCTTTAGACTCAAATGCTTAGGGAACGT
TTCATTTCTCATTCATGGGGAAAGGCAGCCTCCTTAAATGTTTTCTGAAG
AGCGGTAAAATCTAGAAGCTTAAGAATTTACAGTTCCTTCAATAACCATGA
TGACCTGAAGTTCACCTATCCCATTTTAGCATCTACTTGTTTTTCCCATCT
CTTCCTTTCCAATTTTGCTTATACTGCTGTAATATTTTTGTNNNNNNNNNN
NNNNNNNNNNNNNNGACCAGCTAAAATTTTCGACTTGACTTTTTAACTT
AACTCATGAATTAATTAAAGCAAATGAAAAAATTAAAAAGTGTGACTTTTT
CTCGGAGCATATATGTAGCTTTTAGGAAAGGCTGATGATGGTATAAAGTT
TGCTCATTAAGAAAAAAAGACAAGGCTGATTTTGAAGAGAGTTGCTTTTG
AAATAAAATGATCA

Genbank ID: X63657
Description: H.sapiens fvt1 mRNA
Search for GDB entry

3. WI-7336:

Database ID: UTR-04664 (Also known as PI5, G00-679-135, G06527, 7336, U04313)
Source: WICGR: Primers derived from Genbank sequences
Chromosome: Chr18

Primers:
Left = AGACATTCTCGCTTCCCTGA
Right = AATTTTGACCCCTTATGGGC
Product Length = 332
Review complete sequence:

TAAGTGGCATAGCCCATGTTAAGTCCTCCCTGACTTTTCTGTGGATGCCG
ATTTCTGTAAACTCTGCATCCAGAGATTCATTTTCTAGATACAATAAATTG
CTAATGTTGCTGGATCAGGAAGCCGCCAGTACTTGTCATATGTAGCCTTC

ACACAGATAGACCNNNNNNNNNNNCCAATTCTATCTTTTGTTTCCTTTTTT
CCCATAAGACAATGACATACGCTTTTAATGAAAAGGAATCACGTTAGAGG
AAAAATATTTATTCATTATTTGTCAAATTGTCCGGGGTAGTTGGCAGAAAT
ACAGTCTTCCACAAAGAAAATTCCTATAAGGAAGATTTGGAAGCTCTTCT
TCCCAGCACTATGCTTTCCTTCTTTGGGATAGAGAATGTTCCAGACATTC
TCGCTTCCCTGAAAGACTGAAGAAAGTGTAGTGCATGGGACCCACGAAA
CTGCCCTGGCTCCAGTGAAACTTGGGCACATGCTCAGGCTACTATAGGT
CCAGAAGTCCTTATGTTAAGCCCTGGCAGGCAGGTGTTTATTAAAATTCT
GAATTTTGGGGATTTTCAAAAGATAATATTTTACATACACTGTATGTTATA
GAACTTCATGGATCAGATCTGGGGCAGCAACCTATAAATCAACACCTTAA
TATGCTGCAACAAAATGTAGAATATTCAGACAAAATGGATACATAAAGACT
AAGTAGCCCATAAGGGGTCAAAATTTGCTGCCAAATGCGTATGCCACCA
ACTTACAAAAACACTTCGTTCGCAGAGCTTTTCAGATTGTGGAATGTTGG
ATAAGGAATTATAGACCTCTAGTAGCTGAAATGCAAGACCCCAAGAGGAA
GTTCAGATCTTAATATAAATTCACTTTCATTTTTGATAGCTGTCCCATCTG
GTCATGTGGTTGGCACTAGACTGGTGGCAGGGGCTTCTAGCTGACTCG
CACAGGGATTCTCACAATAGCCGATATCAGAATTTGTGTTGAAGGAACTT
GTCTCTTCATCTAATATGATAGCGGGAAAAGGAGAGGAAACTACTGCCTT
TAGAAAATATAAGTAAAGTGATTAAAGTGCTCACGTTACCTTGACACATAG
TTTTTCAGTCTATGGGTTTAGTTACTTTAGATGGCAAGCATGTAACTTATA
TTAATAGTAATTTGTAAAGTTGGGTGGATAAGCTATCCCTGTTGCCGGTT
CATGGATTACTTCTCTATAAAAAATATATATTTACCAAAAAATTTTGTGACA
TTCCTTCTCCCATCTCTTCCTTGACATGCATTGTAAATAGGTTCTTCTTGT
TCTGAGATTCAATATTGAATTTCTCCTATGCTATTGACAATAAAATATTATT
GAACTACC

Genbank ID: G06527
Description: WICGR: Random genome wide STSs

4. WI-8145:

Database ID: EST102441 (Also known as D18S1234, G00-677-827, G06845, 8145, T49159)
Source: WICGR: STSs derived from dbEST sequences
Chromosome: Chr18

Primers:
Left = GAAATGCACATAACATATATTTGCC
Right = TGCTCACTGCCTATTTAATGTAGC
Product Length = 184
Review complete sequence:

GTTGTTTGGANGCAGGTTTATTTATTATATACTTGCAATTGAATATAAGAT
ACAGACATATATATGTGTTATGTATTTCTAGAAATGCACATAACATATATTT
GCCTATTGTTTAATGTTTTTTCCAGANATTTATTACAGAAGGGCATGGAG
GGATACCTACTTATTCTTCATTATGAGAACAATTAAAGGCATTTATTAGAT
AGGAAATTAACAGANCATCTGCTTCTATAACTTTATTAGCTACATTAAATA
GGCAGTGAGCANTAATTTAAAANCTCACCATTATATAAANTANTAAATACC
AAAGTAAAAG

_____: left and right primer

PCR Conditions

Genbank ID: T49159
Description: yb09e07.s1 Homo sapiens cDNA clone 70692 3' similar to gb:J02685
UniGene Cluster Description: Human mRNA for Arg-Serpin (plasminogen activator-inhibitor 2, PAI-2) Search for GDB entry

5. WI-7061:

Database ID: UTR-02902 (Also known as PAI2, G00-678-979, G06377, 7061, M18082)
Source: WICGR: Primers derived from Genbank sequences
Chromosome: Chr18

Primers:
Left = TGCTCTTCTGAACAACTTCTGC
Right = ATAGAAGGGCATGGAGGGAT
Product Length = 338
Review complete sequence:

AACTAAGCGTGCTGCTTCTGCAAAAGATTTTTGTAGATGAGCTGTGTGCC
TCAGAATTGCTATTTCAAATTGCCAAAAATTTAGAGATGTTTTCTACATAT
TTCTGCTCTTCTGAACAACTTCTGCTACCCACTAAATAAAAACACAGAAAT
AATTAGACAATTGTCTATTATAACATGACAACCCTATTAATCATTTGGTCT
TCTAAAATGGGATCATGCCCATTTAGATTTTCCTTACTATCAGTTTATTTT
TATAACATTAACTTTTACTTTGTTATTTATTATTTTATATAATGGTGAGTTTT
AAATTATTGCTCACTGCCTATTTAATGTAGCTAATAAAGTTATAGAAGCAG
ATGATCTGTTAATTTCCTATCTAATAAATGCCTTTAATTGTTCTCATAATGA
AGAATAAGTAGGTATCCCTCCATGCCCTTCTATAATAAATATCTGGAAAAA
ACATTAAACAATAGGCAAATATATGTTATGTGCATTTCTAGAAATACATAA
CACATATATATGTCTGTATCTTATATTCAATTGCAAGTATATAATAAATAAA
CCTGCTTCCAAACAACNNNNNNNNNNNNNGGAATTC

PCR Conditions

Genbank ID: G06377
Description: WICGR: Random genome wide STSs

6. D18S68:

Database ID: AFM248YB9 (Also known as 248yb9, Z17122, D18S68)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = ATGGGAGACGTAATACACCC
Right = ATGCTGCTGGTCTGAGG
Product Length = 285
Review complete sequence:

AAAGAGTTGGGGTTGTGAATTCCCACACCAGTCAACTATTGGCTATGGG
CTTACCATGGGAGACGTAATACACCCGGNACTTCCAACTCACATACCAG
AGACATGGCTCTAGCACCCAATGGAAATATGCTGAATGTTGCAGGTGCA
AGACAGCAACAAAGCAGACAGAGGCACATAGACAAGGCACCAACAGTGT
CCACTATACCCTGACAGTGTGGAAAGTTGTAGATAGGATGAAGAGAAAG
AATACACACACACACACACACACACACACACACACACACACACACACACA
CGGTAGANACTTACTACNCAAAGTGTGANCCTCAGACCAGCAGCATCTG
GCNAAATGGTGATCTATCACCTTCCAG

Genbank ID: Z17122
Description: H. sapiens (D18S68) DNA segment containing (CA) repeat; clone

7. WI-3170:

Database ID: MR3726 (Also known as D18S1037, G04207, HALd22f2, 3170)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = TGTGCTACTGATTAAGGTAAAGGC
Right = TGCTTCTTCAATTTGTAGAGTTGG
Product Length = 156
Review complete sequence

CTGAGACAAGGCAGGCAAACAACCTCTAAAAATCTACAATTGGTGATTGG
TGTGCTACTGATTAAGGTAAAGGCACAGAATTATACATCCAGGTTNCTAT
TACTTATGGCAGACTCAGGACCCAGGTTNAGAGACCACTGGCCTTAAGA
AAAAAAATGGGGTTCCTGATTTCTGGATAATAATCCAACTCTACAAATTGA
AGAAGCAACATACCCTCTTTGTTA

Genbank ID: G04207
Description: WICGR: Random genome wide STSs

8. WI-5654:

Database ID: MR10908 (Also known as D18S1259, G00-678-695, G05278, 5654)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = CTTAATGAAAACAATGCCAGAGC
Right = TGCAAAATGTGGAATAATCTGG
Product Length = 149
Review complete sequence:

CTACAAAATGCATGTGGCTTTGGCTTTGAAATAGTACACCCTATCAAAGA
CTAAATTTTCTTAATGAAAACAATGCCAGAGCTTTTTTCATGATATTTTGTT
TTTAGAGATGGGGAACAATCTGGACGTTGTTTCCTTATCTGGGTGGTAAT
CGAGGCTTAGCAATTTCCCACAGCGTTACACAAATCCAGATTATTCCACA
TTTTGCAAATA

Genbank ID: G05278
Description: WICGR: Random genome wide STSs

9. D18S55:

Database ID: AFM122XC1 (Also known as 122xc1, Z16621, D18S55, GC378-D18S55)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18
Primers:
Left = GGGAAGTCAAATGCAAAATC
Right = AGCTTCTGAGTAATCTTATGCTGTG
Product Length = 143
Review complete sequence:
AGCTGAACATGCCTTTTCATGGAGCAGTTTCNAAATACACTTTTGGTACA
ATCTGCAGGTGGATATTTGGAGCTCAGGAGTTTGAGACCAGCCTGGGCA
ACATGGTGAAATCCCGTCTCTACTAAAATACAAAAAATTAGCCAGGTGTG
GCGGCATGTGCCTGTAGNCCCAGGATGGATTGAGTGGGTGAGATATGG
AATAAGTGGTGGGAAGTCAAATGCAAAATCAATTCAGTTTGTCAATATTG
ATTCTCTATTCTAGCCTGGCGTGGTTTTTCCTCGTCACACACACACACAC
ACACACACACACACACACACACACACACACACACACACACACACACACAGA
AGCT

Genbank ID: Z16621
Description: H. sapiens (D18S55) DNA segment containing (CA) repeat; clone

10. D18S969:

Database ID: GATA-P18099 (Also known as G08003, CHLC.GATA69F01, CHLC.GATA69F01.P18099)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = AACAAGTGTGTATGGGGGTG

Right = CATATTCACCCAGTTTGTTGC
Product Length = 365
Review complete sequence:

CAGGGAAATGCAAATCAAAACCACAATGAGTTATCTCCTCATACCTTTAAT
GATGGCTAATATTAAACAAGAGATAACAAGTGTGTATGGGGGTGTGGAG
AAAAGAGAATGTNCGAACACTCTTGGTTGAAATATAAGTTGGTAGANCCA
TTATGCAAAACAGTATGAATCTTTATCAGTATAANATTAGGACCTNGCATA
TGATCNCAGCAATCNCCACNTCTGNGNGATCNCACNCNCTATCTCTCTAT
ATCTATCTATCTATCTATCTATCTATCTATCTATCTATCTATCTATCTATCT
ATCTGTCTGTCTATCATCTATCTATCTTCTATCTATCTATCTATCTTTCTAT
CTATCTATCTGTCTATCTATNCCGGAATATTTTTCAGCCATNNAAATAAGG
AAGTCCTGCTATTTGCAACAAACTGGGTGAATATGGAGAACGTTATGCTA
AATGCAATATGCTAAAGACAGACACAGAAAGACAAGTATGACCTCACTTA
TATGTGGAAACTGAAAAAGCCATACTCATTACAGCAAAGAGTAGAATGTT
GGTTACCAGGGGCAAAGAGGGTAGAAATGAGGGGAGTGAGAAAATGTC
AATCAAAGTGTAAGAATGTTATAACATAAATAAATTCATAGAG

Genbank ID: G08003
Description: human STS CHLC.GATA69F01.P18099 clone GATA69F01.

11. D18S1113:

Database ID: AFM200VG9 (Also known as D18S1113, 200vg9, w2403)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = GTTGACTCAAGTCCAAACCTG
Right = CAAAGACATTGTAGACGTTCTCTG
Product Length = 207
Review complete sequence:
AGCTGCATATAAAACTATTCCATTTCACATTTTTGAAGACATTTGTAGCCA
TGATACTTTGCTGTTGTCTGTGGGCCACCTCTTTTTGAAGTGTGTAGTTA
ACTGTGCTCCTGTAATCTGTTGTCTGTTGACTCAAGTCCAAACCTGTTCT
GCGTGGCATGTTTCTNCAACTTGATGTGATGCTATTTATCACTTTCTTTGA
AGTTAAGTCTCTATGTCTTTGTATTCTTTCTGTGTACCCAGGGATATGTTT
GTGCATGCACACGCATAAACACACACACACACACACACACACACAGAGA
CAGAGACAGAGAACGTCTACAATGTCTTTGTGAG

12. D18S868:

Database ID: GATA-D18S868 (Also known as G09150, CHLC.GATA3E12, CHLC.GATA3E12.496, CHLC.496, D18S868)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = AGCCAATACCTTGTAGTAAATATCC
Right = GATTCTCCAGACAAATAATCCC
Product Length = 189
Review complete sequence:
GAGTGAGCCAATACCTTGTAGTAAATATCCATCTATCTTTGATGTATCTAT
GTATCTATCTTTGTATCTATATGTCTATGTATCTATGTATGTATGTATCTAT
CTATCATCTATCTATCTATCATCTATCTATCTATCTATCTATCTATCTATCT
ATCTATCTATATCCNTTTGGGATTATTTGTCTGGAGAATCCTGATTAACAT
AGTCTGCTAACTTTTATCTGTATCTCCTATGTGTATGCTTCTCCTTCTTCC
TGTCTCTCTCTCTTCTTTGTCCTCATTTAANCTCCTTTCCTGGGNATATTG
GNAATTTTGATTGGANTCTGGACANTGTAGGAGTAAAAATTT

Genbank ID: G09150
Description: human STS CHLC.GATA3E12.P6553 clone GATA3E12.

13. WI-9959:

Database ID: MR12816 (Also known as D18S1251, G00-678-524, G05488, 9959)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = TGCCAACAGCAGTCAAGC
Right = AGCACCTGCAGCAGTAATAGC
Product Length = 110
Review complete sequence:
ctgttttatttgaaaaaaaaaatctgtctccaagaagaaaagttcattctACCTGTTGCCAACAGC
AGTCAAGCGGACATGTTTAAAATTTTTTAAAAAAGTATTTTTTTTTCCAACT
GGNGTTTAATAGCCTCATTTTGGCTTTTGCTATTACTGCTGCAGGTGCTT
TNATTTTTTTCCTCTGCATTATAATTAC

Genbank ID: G05488
Description: WICGR: Random genome wide STSs
Search for GDB entry

14. D18S537:

Database ID: CHLC.GATA2E06.13 (Also known as CHLC.13, GATA2E06, D18S537, GATA-D18S537)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = TCCATCTATCTTTGATGTATCTATG
Right = AGTTAGCAGACTATGTTAATCAGGA
Product Length = 191

Review complete sequence:
AAAGCTGAGTGAGCCAATACCTTGTAGTAAATATCCATCTATCTTTGATGT
ATCTATGTATCTATCTTTGTATCTATATGTCTATGTATCTATGTATGTATGT
ATCTATCTATCATCTATCTATCTATCATCTATCTATCTATCTATCTATCTAT
CTATCTATCTATCTATATCCNTTNGGTATTATTNGTCTGGNGAATCCTGAT
TAACATAGTCTGCTAACTTNTATCTGTATCTNCTATGTGTATGCTTCTNCT
TCTTCCTGTCTCTCTCTCTGCTTTGTCCTCAATTNAAATCTCC

Genbank ID: G07990
Description: human STS CHLC.GATA2E06.P6006 clone GATA2E06.
Search for GDB entry

15. D18S483:

Database ID: AFM324WC9 (Also known as 324wc9, Z24399, D18S483)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = TTCTGCACAATTTCAATAGATTC
Right = GAACTGAGCAAACGAGTATGA
Product Length = 214
Review complete sequence:
AGCTCTGCTGGAAGAGCAGGGCTGTTTTCTGCACAATTTCAATAGATTCC
CCTACCCTGGGTTTTTCAGTAGATAGATAGATAGATGATAGATAGGTAGA
TAGATAGATAGATAGATAGATAGATAGATAGATAGATGATAGATAGATTTT
ATATATAGTATATAAAATCTACACACACACACACACACACACACACACATA
TTTGCCTTTCCTTGACTATCATACTCGTTTGCTCAGTTCTTTTTTTTTTTAA
ATTTTTGTTTGTAAATCCAAAATGCTT

Genbank ID: Z24399
Description: H. sapiens (D18S483) DNA segment containing (CA) repeat; clone
Search for GDB entry

16. D18S465:

Database ID: AFM260YH1 (Also known as 260yh1, Z23850, D18S465)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = ATATTCCCCTATGGAAGTACAG
Right = AAAGTTAATTTTCAGGCACTCT
Product Length = 232
Review complete sequence:
AGCTCTGTCCCTCTAGAGAACGCTGACTAATATATTCCCCTATGGAAGTA
CAGATGGTTTTTNTAAAATAAATTTATCTGATTGTGATGAGATAATCATCA

TTTTTATGTTCAGTGTTTTTCTAAATTTTTTATTGTTATTGTTTTTATACTCT
AAATGGTTTTTAAATATGCACATATGTGCATATTTTACACACACACACACA
CACACACACACTCTCTTTATTTAGAAGCATTATAGATAGAGTGCCTGAAAA
TTAACTTTTAACCNAAGAAAAGACAATAAGGAACAATAGGGAAGTTATCC
TTTGCTAAGGGTATGGAAAATATTCACATATTATTTATAACANGTTAAACC
AAGTCATGCTTGANTATAATAGCT

Genbank ID: Z23850
Description: H. sapiens (D18S465) DNA segment containing (CA) repeat; clone
Search for GDB entry

17. D18S968:

Database ID: GATA-P34272 (Also known as G10262, CHLC.GATA117C05, CHLC.GATA117C05.P34272)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = GAAATTAACCAGACACTCCTAACC
Right = CTTAGAATTGCCTTTGCTGC
Product Length = 147
Review complete sequence:
GAATAAAAATATGAGGTATTAGAAATTTACAGATAGGAAGAAATTAACCAG
ACACTCCTAACCACCGATNAGTTTAAAGAGGAGATAGATAGATAGATGAT
AGATAGATAGATAGATAGATAGATACCACTGAAAATGCAANCACAAATTA
GCAGATTATATGTGATGCAGCAAAGGCAATTCTAAGTAGATTCTAACTGC
TACATTGATAGCAGTACCCACTGACATTACCGGAAAGGATGGTATCCATA
ACCACCTACCTATATACCTCCGCAGCTGGANATTAGGNTTAAGCTTCTTN
GGGCNCCTGGCGGCCCCNNTTGTGGTCCCCGGTNGGNCCCCGNTTNN
GNNTNGCTNNGNTTNCNTTGGNGNCCCCCNNTNGGTTTNNGGNNNNNT
NNNNNTNGNNNNNTTNCCCNNNNNNNNTNTNNNNCNNNNNNNNTNNN
NNNNNNNNNNGGNNNNNGGGN

Genbank ID: G10262
Description: human STS CHLC.GATA117C05.P34272 clone GATA117C05.

18. GATA-P6051:

Database ID: GATA-P6051 (Also known as CHLC.GATA3E08, CHLC.GATA3E08.P6051)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = GCAACAACCCTAATGAGTATACG

Right = GAGTCTCACCAGGGCTTACA
Product Length = 149
Review complete sequence:
AAAGCTGTCTCCTTTTGTAAAGTGTGCTCAGAGGAATCTTTTTCAGTAAAT
AAAGTCTGCACCCAGACATCTCACTTTGTATACCACGGAGAATTTACCAT
GACTCTTCTCAGTGATAAACGTCAATATAGAATAATCAGGAGAAAAAGAG
AAATCCAGTAAAGAAATAAGTCTGTAGAAAGCAACAACCCTAATGAGTAT
ACGATATCTATCTATCTATCTATCTATCTATCTATCTATCTATCTATCTATG
NATCTATCTATCTAACATTATATAAAATATATATTTCCTCCTGTATTGGGG
CCCTGTGTGTAAGCCCTGGTGAGACTCAAAAATTTGANTATTCCTNTTTN
T

Genbank ID: G09104
Description: human STS CHLC.GATA3E08.P6051 clone GATA3E08.

19. D18S875:

Database ID: GATA-D18S875 (Also known as G08001, CHLC.GATA52H04, D18S875)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = TCCTCTCATCTCGGATATGG
Right = AAGGCTTTCAGACTTACACTGG
Product Length = 394
Review complete sequence:
TTATTTATTCACTCATTCAATAAATATTTATGAATTTCCTTTAATGGCNANG
AAAGTATGTTTGGTACTGAATATGGTGAGCAAGATTTTCCTCTCATCTCG
GATATGGAAAGATCTTGGAAATCATTATACNTCATACTTACAATANGAAAG
AAGCTGAGCAATTTGAAAATCAACAATTTCTTTTGTACNTGTCAGAAAAGT
GAAGATATATTAATCAGGGTTCTTCAGAGAAACATAACCAATAGGNCACA
GNTCTATATGNCCNCNTTTATCTATCTATCTATCTATCTATCNCTATCTAT
CNCANACCNGGNGAANTNATNTTTGNGAGATTNATGCAAGNCTGAGAAA
NACCNAAGAANCTGCTCCCTGTNAAACTNGAGATNCAAGAANCTGAANA
GTATAGNTCCAGTCCNAAGTCTANAGACCTTAGAATTAGGAAAACTGATA
CTATAAATACCAGTGTAAGTCTGAAAGCCTTAAANACCANATAGTGCCAT
TGAAAGGGCAGAAGACTGATGTCCCAGTTCAAGCAGGCAAAGTTAGAGA
AGCCTTATTTTCTGCAACATTGTTCTATTCAGACCCTTNANANGATTGACN
ATGTCCACCCA

Genbank ID: G08001
Description: human STS CHLC.GATA52H04.P16177 clone GATA52H04.
Search for GDB entry

20. WI-2620:

Database ID: MR1436 (Also known as G03602, D18S890, HHAa12h3, 2620)
Source: WICGR: Random genome wide STSs

Chromosome: Chr18

Primers:
Left = TCTCCAAGCTATTGATTGGATAA
Right = TTAAGAGCCAATTTATATAAAAGCAGC
Product Length = 177
Review complete sequence:
CCCCTTTTGCCAACGCCATGCTTCACGTAGGGAGCCTGACATGCAGAAA
ACTCTCCAAGCTATTGATTGGATAAAGAGCCAGAGCTGACTGAATTCCAT
TCTTCTTGAGCCTCTCATTCTGTGTTTCTCGAATTTTTACCAAAGCATCTT
GACACACAAATATCTGACTCAAGGAAAAGGAAAAACAACTGCTTTTTCTC
CAGCTGCTTTTATATAAATTGGCTCTTAAACTTTCTAAGTTTATTATGGAT
A

Genbank ID: G03602
Description: WICGR: Random genome wide STSs
Search for GDB entry

21. WI-4211:

Database ID: MR6638 (Also known as G03617, D18S980, 4211)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = ATGCTTCAGGATGACGTAATACA
Right = AAATTCTCGCTGATTGGAGG
Product Length = 113
Review complete sequence:
CTAGTACCATAATCCCTTTTGGAATAAACCATCCCACCTTTAGTCAGANC
AGATGCTTCAGGATGACGTAATACATAATAAGCCTACTCAGTTCTACTCT
GGCTTTGTATGTCTTCAAAGTGATATTTTTTTAAGTATTACTTGTCCCTCC
AATCAGCGAGAATTT

Genbank ID: G03617
Description: WICGR: Random genome wide STSs
Search for GDB entry

22. D18S876:

Database ID: GATA-D18S876 (Also known as G09963, CHLC.GATA61E10, D18S876)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = TCAAACTTATAACTGCAGAGAACG
Right = ATGGTAAACCCTCCCCATTA

Product Length = 171
Review complete sequence:
AAGACTGCAATTACATTTGCATCAAACTTATAACTGCAGAGAACGTTGCC
CACTATTTTATACCACACAACAGTATTCTTAGCCAGATTACATCTATCTAT
CTATCTATCTATCTATCTATCTATCTATCTATCTATCTATCATCTATCTAGC
TAGCTATCTATCTATAGAACTAATGGGGAGGGTTTACCATGTTTGGGTGA
ACCCAAACATTTTATGGNCAAGGGNTTGGAAAATTACCCTTATCTACAAC
TNTTNAACTTGTTTTGGTAGGNGTGNTAATTCCNTGGGNTTGGAANAACT
TTTGNAATTTCCTCNTTGTTTNTNATTNNNNATTNNTNNNCATTATTNTGG
GGTNTTCNGGGTGGAGGGCTNANTTTGGCCNCCCGGGTCCNNGGNGC
NAGTNGGNNNGGNTNNTNGGGTTTNCTTGGGAANCNTNCCNCCTNCNG
GGGNTTCANGGGNTTTTTNTTTNNTTG

Genbank ID: G09963
Description: human STS CHLC.GATA61E10.P17745 clone GATA61E10.
Search for GDB entry

23. GCT3G01:

Database ID: GCT-P10825 (Also known as G09484, CHLC.GCT3G01, CHLC.GCT3G01.P10825)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = CTTTGCAATCTTAGTTAATTGGC
Right = GAACTATGATATGGAGTAACAGCG
Product Length = 128
Review complete sequence:
AGATGTTTAACTTTGCAATCTTAGTTAATTGGCAGAAATGAAATTTAGTTT
CCACAACTTTTATTCGATATTAAAACACCACCACCATCAGCAGCAGCAGC
AGCAGCAGCAGCATCGCTGTTACTCCATATCATAGTTCAGAGCATTTAAA
GNGGTCAAAATATACAACTAGGCTGACACCNGNATAAGGTTTAATTTTAA
ACCNGNGGTCTNCCCTCTAAGGNGGNTTTTTTTTTCTTGNCNTGGCTTCT
TTTTCCNTTTGCTTTTGTAAAATATCAAGGNATTTTTGGGTTNTTCNTGGN
ANTTNNCNNANTNNTNNTTNNNCNCNCCCCCCNTTTGNGGCGGGGGTC
CCCNNNTTGCCCCGGGGTTGNGTGCAGTAGGGGGGTCNCGGGTNNNG
NAAGTTTNGGGGCCCT

Genbank ID: G09484
Description: human STS CHLC.GCT3G01.P10825 clone GCT3G01.

24. WI-528:

Database ID: MH232 (Also known as G03589, 528, D18S828)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = TTCTGCCTTTCCTGACTGTC
Right = TGTTTCCCATGTCTTGATGA
Product Length = 211
Review complete sequence:
CTACTAAGCAAATTCTGCTCAGCCTTCTGCCTTTCCTGACTGTCTTGTTG
GCCCTTCCCACTTTAAGGATGCCTGTTTAAGTAGCCACCTCTAATTAGGA
ATCTTCCCTTGTTCTTTCTCAGGAGGCTTAGACACTGTCAGTTTCCTGAA
GACAGAAAATAAGCCTGCATTATCCTAGTAGTGGATTCAAAACTAATTGT
GTCCTGAGTCTTTCAATCATCAAGACATGGGAAACACTCAACAG

Genbank ID: G03589
Description: WICGR: Random genome wide STSs
Search for GDB entry

25. WI-1783:

Database ID: MR432 (Also known as G03587, _shu_31.Seq, 1783, D18S824)
Source: WICGR: Random genome wide STSs
Chromosome: Chr18

Primers:
Left = CCAGTAATTAGACATTGACAGGTTC
Right = TTTTACTAGACAGGCTTGATAAACAA
Product Length = 305
Review complete sequence:
CCAGTAATTAGACATTGACAGGTTCCATACTAGTAATGTAGGGAATAGGG
CTGCTGCTTTTTGGGTTTCCTTGAGTATACTTTGTGCTGCATAAATATGG
CAATGGATAGTAAATAATTTGTATGCAGACCTTTAGTGTCGATTAACCTGT
GAATAAGGGAACAACAATCAAGGACAAAAATCAAAAGACTAATTCTCTAT
ACATTTTGAGCTTTTGTAAAAAAGTAAGATTAGCTGAATATATCTGAAAAA
TTTCTAATCTCCTTTACAATTTTTTAAATTGTTTATCAAGCCTGTCTAGTAA
AAATAATTCAGTTTCGGAATGTGG

Genbank ID: G03587
Description: WICGR: Random genome wide STSs
Search for GDB entry

26. D18S477:

Database ID: AFM301XF5 (Also known as 301xf5, Z24212, D18S477)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = GGACATCCTTGATTTGCTCATAA
Right = GATTGACTGAAAACAGGCACAT

Product Length = 243
Review complete sequence:
GGACATCCTTGATTTGCTCATAATACACTCATTCCTTTCACCATTGAGTGT
GCACATATTTCTCTGATTGGAAAGAACTACAGAGGAGGTTTTACNTTTTA
CTTTCCAGTTTGCTATTAAAGAGAGAAAACTAACAGAGNGAAATCAAGCA
ACTCAAAACAACCTTACACACACACACACACACACACACTCACAAAGATA
TTTTGTTCACCATATGTATTGATGTGCCTGTTTTCAGTCAATCCACAGGAA
GGGCTAAGGAGAGTGACATCTGGGCTACATTAAAAGGACAGTCACATTG
CTCAAAGNACTCAAGTTTAGCCCGAGTACAGTAGCT
Genbank ID: Z24212
Description: H. sapiens (D18S477) DNA segment containing (CA) repeat; clone
Search for GDB entry

27. D18S979:

Database ID: GATA-P28080 (Also known as G08015, CHLC.GATA92C08, CHLC.GATA92C08.P28080)
Source: CHLC: genetically mapped polymorphic tetranucleotide repeats
Chromosome: Chr18

Primers:
Left = AGCTTGCAGATAGCCTGCTA
Right = TACGGTAGGTAGGTAGATAGATTCG
Product Length = 155
Review complete sequence:
CTCTACAGTCTCTNACCTTTGGACTCCAGGACTTTCACCAGCACCCTCAA
CATTCCCACTGGGTTCTCAGGACTTTATAGTTGTACTGAGCCATGCCACT
GGATCCTAGGGTCTCCAGCTTGCAGATAGCCTGCTATGGGACTTAATCT
TTGTAATAAGGTGAGTCAATTCTGCCAATAAACCTACTTTCATCTCTATCT
ATCTATCTATCTATCTATCTATCTATCTATATCTATCATCTATCTATCGAAT
CTATCTACCTACCTACCGTATTAGTTCTGTCTCTCTGGAGN

Genbank ID: G08015
Description: human STS CHLC.GATA92C08.P28080 clone GATA92C08.

28. WI-9340:

Database ID: UTR-05134 (Also known as G06102, D18S1034, 9340, X60221)
Source: WICGR: Primers derived from Genbank sequences
Chromosome: Chr18

Primers:
Left = TGAGAGAACGAAATCTCTATCGG
Right = AGGCAGCAAGTTTTTATAAAGGC
Product Length = 115
Review complete sequence:

ATGTATCTATCCCAATTGAGTCAGCTAGAAACAGTTGACTGACTAAATGG
AAACTAGTCTATTTGACAAAGTCTTTCTGTGTTGGTGTCTACTGAAGTTAT
AGTTTACCCTTCCTAAAAATGAAAAGTTTGTTTCATATAGTGAGAGAACGA
AATCTCTATCGGCCAGTCAGATGTTTCTCATCCTTCTTGCTCTGCCTTTG
AGTTGTTCCGTGATCATTCTGAATAAGCATTTGCCTTTATAAAAACTTGCT
GCCTGACTAAAGATTAACAGGTTATAGTTTAAATTTGTAATTAATTCTACC
ATCTTGCAATAAAGTGACAATTGAATG

Genbank ID: G06102
Description: WICGR: Random genome wide STSs
Search for GDB entry

29. D18S466:

Database ID: AFM094YE5 (Also known as 094ye5, Z23354, D18S466)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = ACACTGTAGCAGAGGCTTGACC
Right = AGGCCAAGTTATGTGCCACC
Product Length = 214
Review complete sequence:
aaatgacactttaaggaggtaacactgtagcagaggcttgaccaccacccagttctcactagcactgagg
atgctctattggttgggttacccacacacgcatagacatgcacacacacagacacacagacacacacac
acacacacacacacaccagatatagcattccaaaccatcaatatgctatgcaatactgcattaacaggtcatg
cctgtggtggcacataacttggcctagaaaatactggggacgtctgcattccctttattatcgaattgacttact
tggcttctgagttttcctcagaagtaatacttcaatacctcttccatttctgccttgancattgtttggggtaccaag
tatagct

Genbank ID: Z23354
Description: H. sapiens (D18S466) DNA segment containing (CA) repeat; clone
Search for GDB entry

30. D18S1092:

Database ID: AFMA112WE9 (Also known as D18S1092, w5374, a112we9)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = CTCTCAAAGTAAGAGCGATGTTGTA
Right = CCGAAGTAGAAAATCTTGGCA
Product Length = 163
Review complete sequence:

agctctcaaagtaagagcgatgttgtaactgactgagttgttttgtgaantttttgnttttggagtcagtggagcat
gttattagatgtaaatttaaacacacacacacacacacacacacacacgagaagtaagtgccaag
attttctacttcggcgcctatatttctatatactgattttctgtatttcccagacttgaatatagattgtctttctgntttat
catagacaatctcataataanttaggcataataaggtaatgaggnttttctgggcttcttttcatcatccctgca
atttgagtctcntttatagntgaantcttctctgtaataacntcttgttttagct

Search for GDB entry

31. D18S61:

Database ID: AFM193YF8 (Also known as 193yf8, Z16834, D18S61)
Source: J Weissenbach, Genethon: genetically mapped polymorphic STSs
Chromosome: Chr18

Primers:
Left = ATTTCTAAGAGGACTCCCAAACT
Right = ATATTTTGAAACTCAGGAGCAT
Product Length = 174
Review complete sequence:
CGTCTTACCAAACCAACATAATATAGCAATGGNAACCAAAAATTTCTAAGA
GGACTCCCAAACTACATTCTTCTNCCTGAATTAAATACAGGCATTCAANA
NAAACANACACACACACACACACACACACACACACACACACACACACGCACA
CCCTTCAAATCNTAGCATAAATTCCNCTTATATAAACATAACCATGCTCCT
GAGTTTCAAAATATTGGGTGGTTCGAAGTTCGAAGCAACAAATTTCCAGT
TAGTGTCTATTANTTGTTGGACAGCT

Genbank ID: Z16834
Description: H. sapiens (D18S61) DNA segment containing (CA) repeat; clone
Search for GDB entry

Markers (STRs) used in refining the candidate region.

Below the markers are shown that were used in family MAD31 to refine the candidate region. Most of these markers are already described above and will therefore only be mentioned to by their name. For the additional markers, the information is given here.

Data was already shown for: D18S68, D18S55, D18S969, D18S1113, D18S483, D18S465, D18S876, D18S477, D18S979, D18S466 and D18S61.

New data:

1. D18S51:

Other names: UT574, (D18S379)
Primer sequences:
UT574a GAGCCATGTTCATGCCACTG
UT574b CAAACCCGACTACCAGCAAC

DNA-sequence:
AATTGAGCNCAGGAGTTTAAGACCAGCCTGGGTAACACAGTGAGACCCC
TGTCTCTACAAAAAAATACAAAAATNAGTTGGGCATGGTGGCACGTGCCT
GTAGTCTCAGCTACTTGCAGGGCTGAGGCAGGAGGAGTTCTTGAGCCCA
GAAGGTTAAGGCTGCAGTGAGCCATGTTCATGCCACTGCACTTCACTCT
GAGTGACAAATTGAGACCTTGTCTCAGAAAGAAAGAAAGAAAGAAAGAAA
GAAAGAAAGAAAGAANGAAAGAAAGAAAGTAAGAAAAAGAGAGGGAAAG
AAAGAGAAANAGNAAANAAATAGTAGCAACTGTTATTGTAAGACATCTCC
ACACACCAGAGAAGTTAATTTTAATTTTAACATGTTAAGAACAGAGAGAAG
CCAACATGTCCACCTTAGGCTGACGGTTTGTTTATTTGTGTTGTTGCTGG
TAGTCGGGTTTGTTATTTTTAAAGTAGCTTATCCAATACTTCATTAACAAT
TTCAGTAAGTTATTTCATCTTTCAACATAAATACGNACAAGGATTTCTTCT
GGTCAAGACCAAACTAATATTAGTCCATAGTAGGAGCTAATACTATCACA
TTTACTAAGTATTCTATTTGCAATTTGACTGTAGCCCATAGCCTTTTGTCG
GCTAAAGTGAGCTTAATGCTGATCGACTCTAGAG

GENBANK ID: L18333

2. D18S346.

Other name: UT575

Primer Pairs:

Primer A: TGGAGGTTGCAATGAGCTG
Primer B: CATGCACACCTAATTGGCG

DNA sequence:
ACGAGGACAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAACCCCGTT
TNTACTAAAANTACAAAANTTGGTCGGGAGGCTGGGGCAGGNGACATGC

TTGACCCCAGGAGGTGGAGGTTGCAATGAGCTGAGATTGCACCACTGCA
CTNCAGCNTGG.....AAGAAAGAGAAAGGANAGNNAGGNAGNNANNAAAC
TACATNTGAAGTCAACACTAGTATTGGTGGGAGAGGAATTTTATGCTGCA
TTCCCCNACAACCACTAGATACGCCAATTAGGTGTGCATGGTCCATGCTA
T

GenBank ID: L26588

3. D18S817.

Other name: UT6365

Primer Pairs:

Primer A: GCAAAGCAGAAGTGAGCATG
Primer B: TAGGACTACAGGCGTGTGC

DNA Sequence:

CATATGGGTCCACAAGCAACCTCAGTCCTTGTCTCTTCAGAAGAAAGAAT
TCTACTGAGGGNCATAAGGCAGAAGGAGAGACCTAGGCAAGTTGCAAAG
CAGAAGTGAGCATGTATTAAAAAGCTTTAGAACAGTAAGGAAAGGAAGAA
AAGAAAAGAAGGAAAGTTCAACTTGGAAGAGGGCCAAGCCGGCAACTTG
GCAGAAGGATTGCTTGAGCCCAGGAGTTAAGACCAGTCTGGGCAATATA
GTGAGACTCCATCTCTGCATACATACATACATACATACATACATACA
TACATACATATTGCAGGGTATGATGGCACACGCCTGTAGTCCTAGCTACT
CTGGAGGTTGAGATGGGAGGGTCACTGAGCCTGGGAANTTGAGGCTGC
NNTGAGCCATGATC

GenBank ID: L30552

Characterisation of YACs.

8 YACs were selected covering the candidate region and flanking the gap. These YACs were further characterised by determining the end-sequences by the Inverse-PCR protocol.
Selected YACs: 961_h_9, 942_c_3, 766_f_12, 731_c_7, 907_e_1, 752_g_8, 717_d_3, 745_d_2

New STSs based on end-sequences (unless indicated otherwise, the STSs were tested on a monochromosomal mapping pannel for identifying chimaerism of the YAC; if the STS revealed a hit not on chromosome 18q - chimaeric YAC- then it is indicated in the text below):

1. SV32L.

Derived from YAC 745_d_2 left arm end-sequence.

Primer A: GTTATTACAATGTCACCCTCATT
Primer B: ACATCTGTAAGAGCTTCACAAACA

DNA-sequence:

ATTCCTTNGTTATTACAATGTCACCCTCATTTAAAAAGTGGAAAGATAAAG
AGGAAGCAATCTATTTTTTTCCTTTTTTTCTGATAGCACTTGTTTGTGAAG
CTCTTACAGATGTTCTTAAGTAAAATCAACTCCTCCATTTTTTTTGTAGCA
ACTACACATATTTATCAATAATAGTTCACAAATACATTTTCAAATT

Amplified sequence length: 107 basepairs (bp)

This STS has no clear hit on the monochromosomal mapping pannel.

2. SV32R.

Derived from YAC 745_d_2 right arm end-sequence.

Primer A: ACGTTTCTCAATTGTTTAGTC
Primer B: TGTCTTGGCATTATTTTTAC

DNA sequence:

AGACAATGGGAGAAATTGCACTGCCCTGAGTCAGAAATCAGATCTGTTG
CCATACAGCTGCCGTTATGTGATCATTTGCAAGTCAACGTTTCTCAATTG
TTTAGTCATTTGTAAGACAAAAAGACTGGTTGGATTTCAGAGAATTTGGA
ATCCTCCTTCAGGTTTAACAAGCAATAAATGATACTCTTCAGTGTAAAAAT
AATGCCAAGACATNATTTGACTTTAAATTAAATCCAAACAAGATATC

Amplified sequence length: 127 bp

This STS has no clear hit on the monochromosomal mapping pannel.

3. SV11L.

Derived from YAC 766_f_12 left arm end-sequence.

Primer A: CTATGCTCTGATCTTTGTTACTTT
Primer B: ATTAACGGGAAAGAATGGTAT

DNA sequence:

GTCTTTATTTCATATAACTATGCTCTGATCTTTGTTACTTTCTCCTTTTAAC
TCAGTTTAAGCTTTATTCTTATTTTCCAGCTGCTGAAGGTATATAGTTAGG
TTGTTTATTGGATACCATTCTTTCCCGTTAATGTCAGTGGTTACTGCTATC
AATGTAGCAGTTA

Amplified sequence length: 118 bp

This STS has a hit with chromosome 18 and must ba located between CHLC.GATA-p6051 and D18S968.

4. SV11R.

Derived from YAC 766_f_12 right arm end-sequence.

Primer A: AAGGTATATTATTTGTGTCG
Primer B: AAACTTTTCTTAACCTCATA

DNA sequence:

ATAAGGTATATTATTTGTGTCGTGAGTTAAGAAATCATTAATAACTATTTT
CAGAATGACAAATGTCATTATATGTTGTAAAAAAGATAAATACGTGAAATT
ATGAGGTTAAGAAAAGTTTA

Amplified sequence length: 119 bp.

This STS has a hit with chromosome 18 and must be located between D18S876 and GCT3G01.

5. SV34L.

Derived from YAC 717_d_3 left arm end-sequence.

Primer A: TCTACACATATGGGAAAGCAGGAA
Primer B: GCTGGTGGTTTTGGAGGTAGG

DNA sequence:

ACATAAAATGTCGCTCAAAAACAATTATGTGTGTCTACACATATGGGAAA
GCAGGAAACAAATTTGTTTACAACATACATTACTTTTGTTTTTTAGGCAAG
ATAAAATNTCCTACCTCCAAAACCACCAGCACNGTCCGCAATAACTATAC
ATC

Amplified sequence length: 98 bp

This STS has a hit with chromosome 18.

6. SV34R.

Derived from YAC 717_d_3 right arm end-sequence.

Primer A: ATAAGAGACCAGAATGTGATA
Primer B: TCTTTGGAGGAGGGTAGTC

DNA-sequence:

AATATCATTCTTCACCCACGTTATACATAAGAGACCAGAATGTGATATTGT
CATCTCACATGGAAAAATCTGCTGTGATCAGTTCCTGAAGCTTGCTGTGA
TCCTCCCTTAGGAAAGTAGAAAAATCTTTTTGAAACACTTTATTCTACAAT
CAATGAAAATTAGGTGAAGCTACAGAAGCCAGAAATTACTCTAAGATTAG
ACAATTATTTAAGANGACCAATTGTCTTTGGTCTTCTTCTGAAGGGTCTG
ACTACCCTCCTCCAAAGAATTCACTGGCCGTCGTTTTACAACGTCNTGA

Amplified sequence length: 244 bp

This STS has a hit with chromosome 1, therefore YAC 717_d_3 is chimaeric

7. SV25L.

Derived from YAC 731_c_7 left arm end-sequence.

Primer A: AAATCTCTTAAGCTCATGCTAGTG
Primer B: CCTGCCTACCAGCCTGTC

DNA sequence:

AGTGGAGAGATAGAAAGAGAGGAAGATTTTTTTTTTTTAAATCTCTTAAGCT
CATGCTAGTGTAGGTGCTGGCAGGTCTGAACACTCTGTAGGACAGGCTG
GTAGGCAGGAA

Amplified sequence length: 72 bp

This STS has no clear hits on the monochromosomal mapping pannel.

8. SV25R.

Derived from YAC 731_c_7 right arm end-sequence.

Primer A: TGGGGTGCGCTGTGTTGT
Primer B: GAGATTTCATGCATTCCTGTAAGA

DNA-sequence:

GGAGGGTGTTNTCACANAAGTCTGGGGTGCGCTGTGTTGTTCATTGTAA
AAACCCTTTGGANCATCTGGGAATGTGCTGCCCCACATGTCCAGGTAAC
GTTCTCAGGAAGGGGAGGCTGGAAATCTCTGTGTGTTCTTACAGGAATG
CATGAAATCTCCCANCCCCTCTTGTTGGAAATTTCCCTCACTTT

Amplified sequence length: 136 bp

This STS has a hit with chromosome 7; therefore YAC 731_c_7 is chimaeric

9. SV31L.

Derived from YAC 752_g_8 left arm end-sequence.

Primer A: GAGGCACAGCTTACCAGTTCA
Primer B: ATTCATTTTCTCATTTTATCC

DNA-sequence:

CTTCTCNATGANTGGACAAATGTCATTGGGTCAGCATGAGGCACAGCTT
ACCAGTTCAGATTCCAGTAGCTGAGGAACAAATCTTAACTCCAAAAATAA
GTAATTGCGTCACTTTGGAGGAATTATTTGACCTTTTCATAACTTTGACAT
CACAACAATGAGGGTGAAGTTAGTAAAATAAATGATTATTATGAGGATAA
AATGAGAAAATGAATTNAGTGCTTAAGACAATGCTTGGTAACTAGTTAAN
CCG

Amplified sequence length: 178 bp

This STS has a hit with chromosome 18 and must be located between D18S876 and GCT3G01.

10. SV31R.

Derived from YAC 752_g_8 right arm end-sequence.

Primer A: CAAGATTATGCCTCAACT
Primer B: TAAGCTCATAATCTCTGGA

DNA sequence:

AAACTTTAACCAATTTAAACTCCCTAACAGTTCTATAAAATAAGCAAGATT
ATGCCTCAACTTTATGGATAAAGAAATGGAGGCATTAAGAGATAACTAAC
TTGCCCAAGGCCACACAAGTGACTGAGTAAGAATTGCAAAGCCAATGAG
TCTGGCTCCAGAGATTATGAGCTTAATCACCACACTGTGCCACCTCCTGT
GTTTCCTGG

Amplified sequence length: 131 bp

This STS has no clear hits on the monochromosomal mapping pannel and gives no information concerning the chimaerity of the YAC.

11. SV10L.

Derived from YAC 942_c_3 left arm end-sequence.

Primer A: TCACTTGGTTGGTTAACATTACT
Primer B: TAGAAAAACAGTTGCATTTGATAT

DNA-sequence:

GGTNTTTCACTTGGTTGGTTAACATTACTTCTAAGTTTTTTATTGTTTTTTA
TGCTATTGCTAATGGGATTGCTTTCTTAATTTATTTTTTCCAATAGCTTGT
TGTTAGTTTATATCAAATGCAACTGTTTTTCTATGCAAATTATGTTTCCT

Amplified sequence length: 130 bp

This STS has a hit with chromosome 18 and must be located between CHLC.GATA-p6051 and D18S968

12. SV10R.

Derived from YAC 942_c_3 right arm end-sequence.

Primer A: AACCCAAGGGAGCACAACTG
Primer B: GGCAATAGGCTTTCCAACAT

DNA sequence:
TTGGTGGTGCCCTAGGTTTGGCAATTATAAATAAAGCTGCTACAAACATT
CATGTGCAGGTCTCCGTGTGGACATAATTTTCCAGTTCATTTGGGTAAAA
CCCAAGGGAGCACAACTGTTGGATCCTATNATAAAAATATNTCTCGTTTC
ATTTAAAAAACCTGGGAAACTATCTNCCCACAGTGGCTGTCCCTTTTTGT
ATCCCCACCAACAATGTTGGAAAGCCTATTGCCANCAT

Amplified sequence length: 135 bp

This STS has a hit with chromosome 18 and must be located between D18S876 and GCT3G01

13. SV6L.

Derived from YAC 961_h_9 left arm end-sequence.

No primer was made, because this sequence is identical to a known STR marker D18S42, which is indeed mapped to this region.

Primer A:
Primer B:

DNA sequence:

CATGNCTCACAGTGTTCTGAGGCTGCTCTGGACATGCAATCTTGCATGC
TTTTGTCATGACAGGTCTTAAANAGTTTATCAGCTTNCTCAAATAGCTGAA
TGACANAACACTGGATTTTTGTTCAAATANCCTATCAACTTGGCNTCTGT
GTTGCGGTTGTCACTTGGTAACAAAATAAGTC

Amplified sequence length:

SV6L recognises D18S42 which must be therefore located between WI-7336 and WI-8145

14. SV6R.

Derived from YAC 961_h_9 right arm end-sequence.

Primer A: TTGTGGAATGGCTAAGT
Primer B: GAAAGTATCAAGGCAGTG

DNA sequence:

TAATTGACAAATAAAAATTGTATATTTTNCATATTTAACATGTTATGCTAAC
ATATATATGGATTGTGGAATGGCTAAGTCAGAAATTCTTTTACATTCATAT
TTCCATATTATTTACTTTNNGCTTTAAAAAATATGTAAATGANAATACTTAT
TTTTTTCAGTGTCACTGCCTTGATACTTTCACATTTNNGTTACATATTATTT
CCCTTNCATCTAACAAATATATATTGAGTTTCTATAATGTGTCTGACACTG
A

Amplified sequence length: 122 bp

SV6R amplifies a segment on chromosome 18. This segment must be located between WI-2620 and WI-4211

15. SV26L.

Derived from YAC 907_e_1 left arm end-sequence.

Primer A: TATTTGGTTTGTTTGCTGAGGT
Primer B: CAAGAAGGATGGATACAAACAAG

DNA sequence:

TGGTCACTGGTGCCTTATTTGGTTTGTTTGCTGAGGTCATATTTCCTGTG
GCCTTCATGCTTGATTTGTTGGAGTCTAGCCATGTAAAANTCTGTTGGAG
TCTAGGCATTTAAAAAATAGGTATTTATTGTAATCTTTGCCATTTGCTTGT
TTGTATCCATCCTTCTTGGGAAGGCTTTACAGGCATTCAAAAGG

Amplified sequence length: 154 bp

This STS has a hit with chromosome 13; therefore YAC 907_e_1 is chimaeric.

16. SV26R.

Derived from YAC 907_e_1 right arm end-sequence.

Primer A: CGCTATGCATGGATTTA
Primer B: GCTGAATTTAGGATGTAA

DNA sequence:

CGCTATGCATGGATTTAAACTGAGTGTAGTGCACTCACTATGTTGCAGTC
TCTTATTCTAGGTTCCTAATATTTACATCCTAAATTCAGCT

Amplified sequence length: 90 bp

no clear hits on monochromosomal mapping pannel: no information concerning chaemerity at this side of the YAC

Testing of 3 end-sequences flanking the gap in additional YACs: STS-markers WI-4211, D18S876 and GCT3G01 are also shown in order to identify YACs on opposite sides of the gap more clearly in table 3 below.

	STSs					
YACs	WI-4211	D18S876	SV31L	SV11R	SV10R	GCT3G01
940_b_1	+	+	+	-	-	-
766_f_12	+	+	+	+	-	-
846_a_5	+	-?	+	+	-	-
752_g_8	+	+	+	+	-	-
745_d_2	+	+	+	+	-	-
961_c_1	+	+	-	-	-	-
942_c_3	+	+	+	+	+	-
717_d_3	-	-	+	+	-?	+
972_e_11	-	-	-	-	-	+
940_h_10	-	-	-	-	+	+
821_e_7	-	-	-	-	+	+
731_c_7	-	-	-	-	-	+
889_c_4	-	-	-	-	+	+
907_e_1	-	-	-	+	+	+

- +: positive hit / -: no hit / ?: 2 instances were observed in which a positive hit was expected (on the assumed order of the markers) but not observed. The reasons for this are not clear.

YAC 745.d.2 was excluded from further analysis since there was no clear hit with chromosome 18. Of the remaining 7 from a monochromosomal mapping panel it was determined that 3 were chimeric and 4 non-chimeric as shown in Table 4 below.

TABLE 4

YAC	chimaeric	chromosome
961_h_9 (6)	no	
942_c_3 (10)	no	
766_f_12 (11)	no	
731_c_7 (25)	yes	chromosome 7
907_e_1 (26)	yes	chromosome 13
752_g_8 (31)	no	
717_d_3 (34)	yes	chromosome 1

For the non-chimeric YACs the STS based on the end-sedquence flanking the gap (10R, 11R, 31L) was tested on 14 YACs flanking the gap. Overlaps between YACs on opposite sides of the gap were demonstrated: e.g. the "11R" end-sequence (766_f_12) detects YAC 766_f_12 and YAC 907_e_1.

YACs were then selected comprising the minimum tiling path:

TABLE 5

YAC	size	chimaerity
961_h_9	1180 kb	not chimaeric
766_f_12	1620 kb	not chimaeric
907_e_1	1690 kb	chimaeric (chr. 13)

These three YACs are stable as determined by PFGE and their sizes roughly correspond to the published sizes. These YACs were transferred to other host-yeast strains for restriction mapping.

CLAIMS:

1. Use of an 8.9 cM region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979 or a fragment thereof for identifying at least one human gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder.

2. Use of a YAC clone comprising a portion of human chromosome 18q disposed between polymorphic markers D18S60 and D18S61 for identifying at least one human gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder.

3. The use as claimed in claim 2 wherein said portion comprises the region of chromosome 18q between polymorphic markers D18S68 and D18S979 or a fragment of said region.

4. The use as claimed in claim 2 or 3 wherein said YAC clone is 961_h_9, 942_c_3, 766_f_12, 731_c_7, 907_e_1, 752-g-8 or 717_d_3.

5. The use as claimed in claim 4 wherein said YAC clone is 961_h_9, 766_f_12 or 907_e_1.

6. The use as claimed in any preceding claim wherein said mood disorder or related disorder is selected from the Diagnostic and Statistical Manual of Mental Disorders, version 4 (DSM-IV) taxonomy and includes mood disorders (296.XX, 300.4,311,301, 13,295.70), schizophrenia and related disorders (295,297.1,298.9,297.3,298.9), anxiety disorders

(300.XX,309.81,308.3), adjustment disorders (309,XX) and personality disorders (codes 301.XX).

7. A method of identifying at least one human gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder which comprises detecting nucleotide triplet repeats in a region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979.

8. A method of identifying at least one human gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder which comprises fragmentation of a YAC clone as defined in any one of claims 2 to 4 and detection of nucleotide triplet repeats.

9. A method as claimed in claim 7 or 8 wherein said repeated triplet is CAG or CTG.

10. A method as claimed in claim 9 wherein said repeated triplet is detected by means of a probe comprising at least 5 CTG and/or CAG repeats.

11. A method of identifying at least one human gene including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder wherein said gene is present in the DNA comprised in the YAC clones as defined in any one of claims 2 to 5, which method comprises the step of detecting an expression product of said gene with an antibody capable of recognising a protein with an amino acid sequence comprising a string of at least 8 continuous glutamine residues.

12. A method as claimed in claim 11 wherein said DNA forms part of a human cDNA expression library.

13. A method as claimed in claim 11 or claim 12 wherein said antibody is mAB 1C2.

14. A method of preparing a contig map of YAC clones of the region of human chromosome 18q between polymorphic markers D18S60 and D18S61 which comprises the steps of:

(1) subcloning the YAC clones according to any one of claims 2 to 5 into exon trap vectors;

(2) using the nucleotide sequences shown in any one of Figures 1 to 11 or any other known sequence tagged sequence from the YAC contig described herein, or part thereof consisting of not less than 14 contiguous bases or the complement thereof, to detect overlaps among the cosmid vectors, and

(3) constructing a cosmid contig map of a YAC clone of said region.

15. A method of identifying at least one human gene or any mutated or polymorphic variant thereof which is associated with a mood disorder or related disorder which comprises the steps of:

(1) transfecting mammalian cells with DNA sequences cloned into an exon trap vector as prepared in claim 14;

(2) culturing said mammalian cells in an

appropriate medium;

(3) isolating RNA transcripts expressed from an SV40 promoter;

(4) preparing cDNA from said RNA transcripts;

(5) identifying splicing events involving exons of the DNA subcloned into said exon trap vector in accordance with claim 14 to elucidate positions of coding regions in said subcloned DNA;

(6) detecting differences between said coding regions and equivalent regions in the DNA of an individual afflicted with said mood disorder or related disorder; and

(7) identifying said gene or mutated or polymorphic variants thereof which is associated with said mood disorder or related disorder.

16. A method of identifying at least one human gene or mutated or polymorphic variants thereof which is associated with a mood disorder or related disorder which comprises the steps of:

(1) subcloning the YAC clones according to any one of claims 2 to 5 into a cosmid, BAC, PAC or other vector;

(2) using the nucleotide sequences shown in any one of Figures 1 to 11 or any other known sequence tagged sequence from the YAC contig

described herein, or part thereof consisting of not less than 14 contiguous bases or the complement thereof, to defect overlaps amongst the subclones and construct a map thereof;

(3) identifying the position of genes within the subcloned DNA by one or more of CpG island identification, zoo-blotting, hybridization of said subcloned DNA to a cDNA library or a Northern blot of mRNA from a panel of culture cell lines;

(4) detecting differences between said genes and equivalent regions of the DNA of an individual afflicted with a mood disorder or related disorder; and

(5) identifying said gene which, if defective, is associated with said mood disorder or related disorder.

17. An isolated human gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder which is obtainable by the method according to any of claims 7 to 13, 15 or 16.

18. A human protein which, if defective, is associated with a mood disorder or related disorder which is the expression product of the gene according to claim 17.

19. A cDNA encoding the protein of claim 18 which is obtainable by the method of any one of claims 7

to 13, 15 or 16.

20. Use of a probe of at least 14 contiguous nucleotides of the cDNA of claim 19 or the complement thereof in a method for detection in a patient of a pathological mutation or genetic variation associated with a mood disorder or related disorder which method comprises hybridizing said probe with a sample from said patient and from a control individual.

FIG. 1.

GTCTTTATTTCATATAACTATGCTCTGATCTTTGTTACTTTCTCCTTTTAAC
TCAGTTTAAGCTTTATTCTTATTTTCCAGCTGCTGAAGGTATATAGTTAGG
TTGTTTATTGGATACCATTCTTTCCCGTTAATGTCAGTGGTTACTGCTATC
AATGTAGCAGTTA

FIG. 2.

ATAAGGTATATTATTTGTGTCGTGAGTTAAGAAATCATTAATAACTATTTT
CAGAATGACAAATGTCATTATATGTTGTAAAAAAGATAAATACGTGAAATT
ATGAGGTTAAGAAAAGTTTA

FIG. 3.

ACATAAAATGTCGCTCAAAAACAATTATGTGTGTCTACACATATGGGAAA
GCAGGAAACAAATTTGTTTACAACATACATTACTTTTGTTTTTTAGGCAAG
ATAAAATNTCCTACCTCCAAAACCACCAGCACNGTCCGCAATAACTATAC
ATC

FIG. 4.

AATATCATTCTTCACCCACGTTATACATAAGAGACCAGAATGTGATATTGT
CATCTCACATGGAAAAATCTGCTGTGATCAGTTCCTGAAGCTTGCTGTGA
TCCTCCCTTAGGAAAGTAGAAAAATCTTTTTGAAACACTTTATTCTACAAT
CAATGAAAATTAGGTGAAGCTACAGAAGCCAGAAATTACTCTAAGATTAG
ACAATTATTTAAGANGACCAATTGTCTTTGGTCTTCTTCTGAAGGGTCTG
ACTACCCTCCTCCAAAGAATTCACTGGCCGTCGTTTTACAACGTCNTGA

FIG. 5.

GGAGGGTGTTNTCACANAAGTCTGGGGTGCGCTGTGTTGTTCATTGTAA
AAACCCTTTGGANCATCTGGGAATGTGCTGCCCCACATGTCCAGGTAAC
GTTCTCAGGAAGGGGAGGCTGGAAATCTCTGTGTGTTCTTACAGGAATG
CATGAAATCTCCCANCCCCTCTTGTTGGAAATTTCCCTCACTTT

FIG. 6.

CTTCTCNATGANTGGACAAATGTCATTGGGTCAGCATGAGGCACAGCTT
ACCAGTTCAGATTCCAGTAGCTGAGGAACAAATCTTAACTCCAAAAATAA
GTAATTGCGTCACTTTGGAGGAATTATTTGACCTTTTCATAACTTTGACAT
CACAACAATGAGGGTGAAGTTAGTAAAATAAATGATTATTATGAGGATAA
AATGAGAAAATGAATTNAGTGCTTAAGACAATGCTTGGTAACTAGTTAAN
CCG

FIG. 7.

GGTNTTTCACTTGGTTGGTTAACATTACTTCTAAGTTTTTTATTGTTTTTTA
TGCTATTGCTAATGGGATTGCTTTCTTAATTTATTTTTTCCAATAGCTTGT
TGTTAGTTTATATCAAATGCAACTGTTTTTCTATGCAAATTATGTTTCCT

FIG. 8.

TTGGTGGTGCCCTAGGTTTGGCAATTATAAATAAAGCTGCTACAAACATT
CATGTGCAGGTCTCCGTGTGGACATAATTTTCCAGTTCATTTGGGTAAAA
CCCAAGGGAGCACAACTGTTGGATCCTATNATAAAAATATNTCTCGTTTC
ATTTAAAAAACCTGGGAAACTATCTNCCCACAGTGGCTGTCCCTTTTTGT
ATCCCCACCAACAATGTTGGAAAGCCTATTGCCANCAT

FIG. 9.

CATGNCTCACAGTGTTCTGAGGCTGCTCTGGACATGCAATCTTGCATGC
TTTTGTCATGACAGGTCTTAAANAGTTTATCAGCTTNCTCAAATAGCTGAA
TGACANAACACTGGATTTTTGTTCAAATANCCTATCAACTTGGCNTCTGT
GTTGCGGTTGTCACTTGGTAACAAAATAAGTC

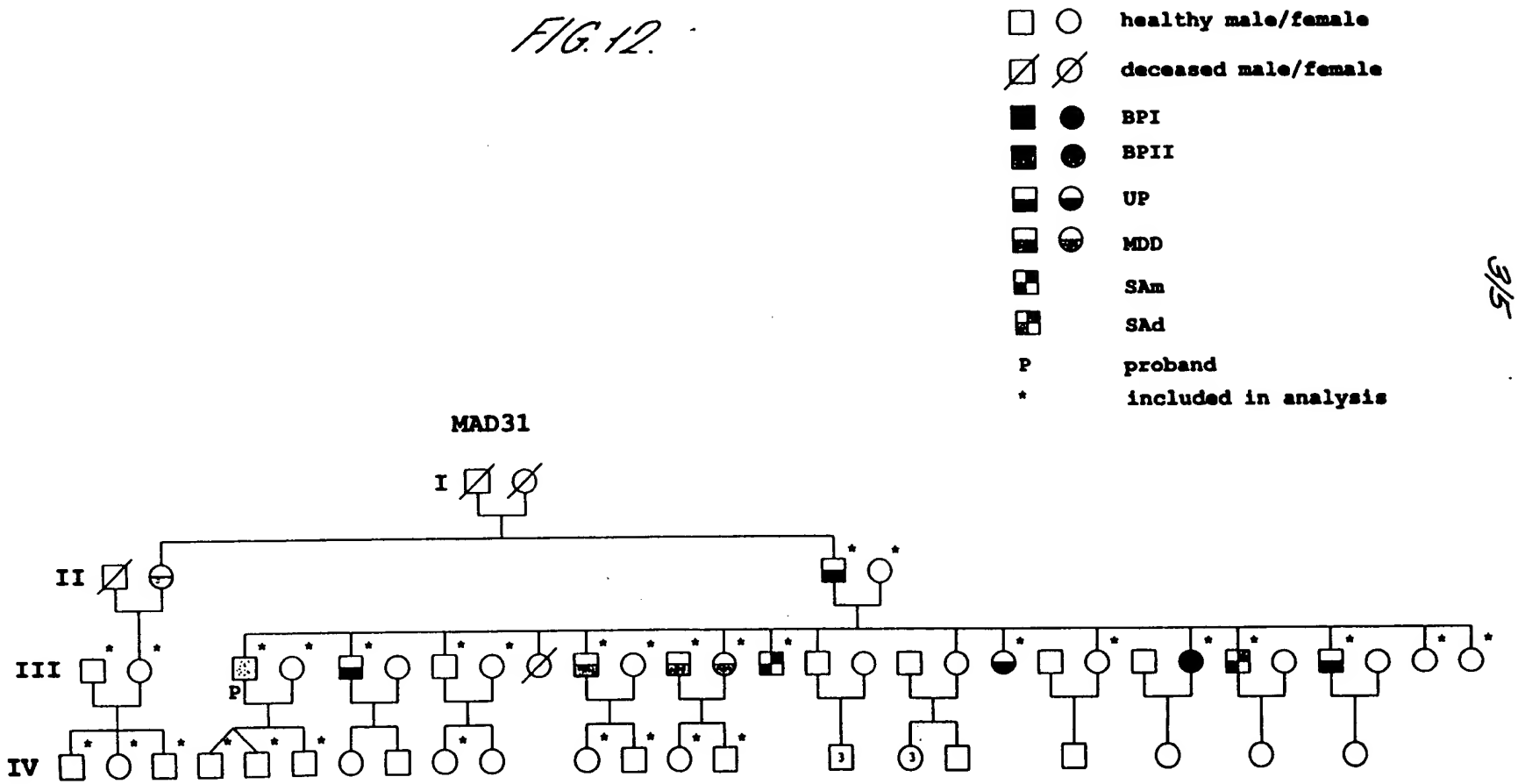
FIG. 10.

TAATTGACAAATAAAAATTGTATATTTTNCATATTTAACATGTTATGCTAAC
ATATATATGGATTGTGGAATGGCTAAGTCAGAAATTCTTTTACATTCATAT
TTCCATATTATTTACTTTNNGCTTTAAAAAATATGTAAATGANAATACTTAT
TTTTTTCAGTGTCACTGCCTTGATACTTTCACATTTNNGTTACATATTATTT
CCCTTNCATCTAACAAATATATATTGAGTTTCTATAATGTGTCTGACACTG
A

FIG. 11.

TGGTCACTGGTGCCTTATTTGGTTTGTTTGCTGAGGTCATATTTCCTGTG
GCCTTCATGCTTGATTTGTTGGAGTCTAGCCATGTAAAANTCTGTTGGAG
TCTAGGCATTTAAAAAATAGGTATTTATTGTAATCTTTGCCATTTGCTTGT
TTGTATCCATCCTTCTTGGGAAGGCTTTACAGGCATTCAAAAGG

FIG. 12.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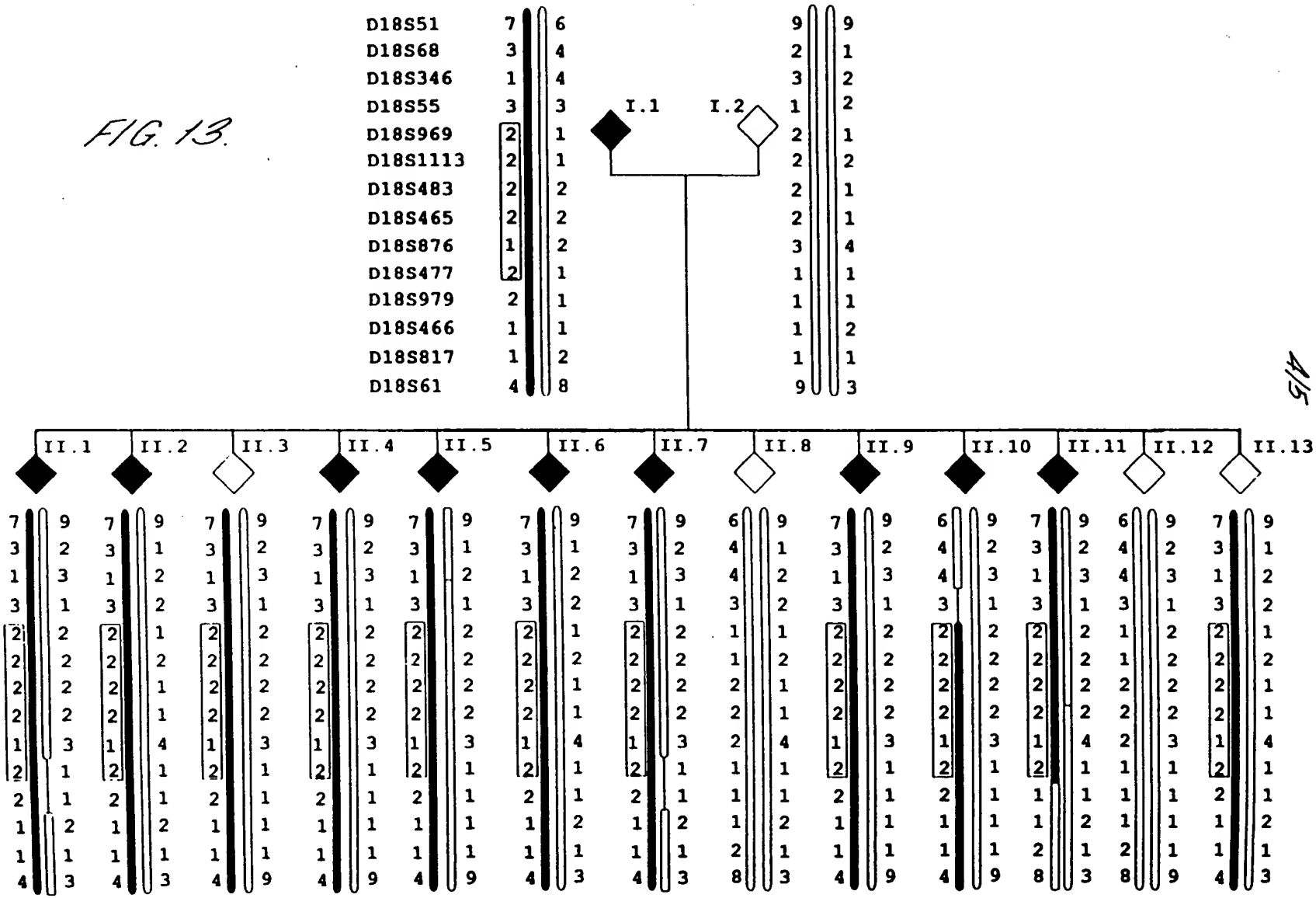
deceased male/female
BPI
BPII
UP
MDD
SAm
SAd
P
proband
*
included in analysis
MAD31
I
II
III
IV
P

FIG. 13.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I.2
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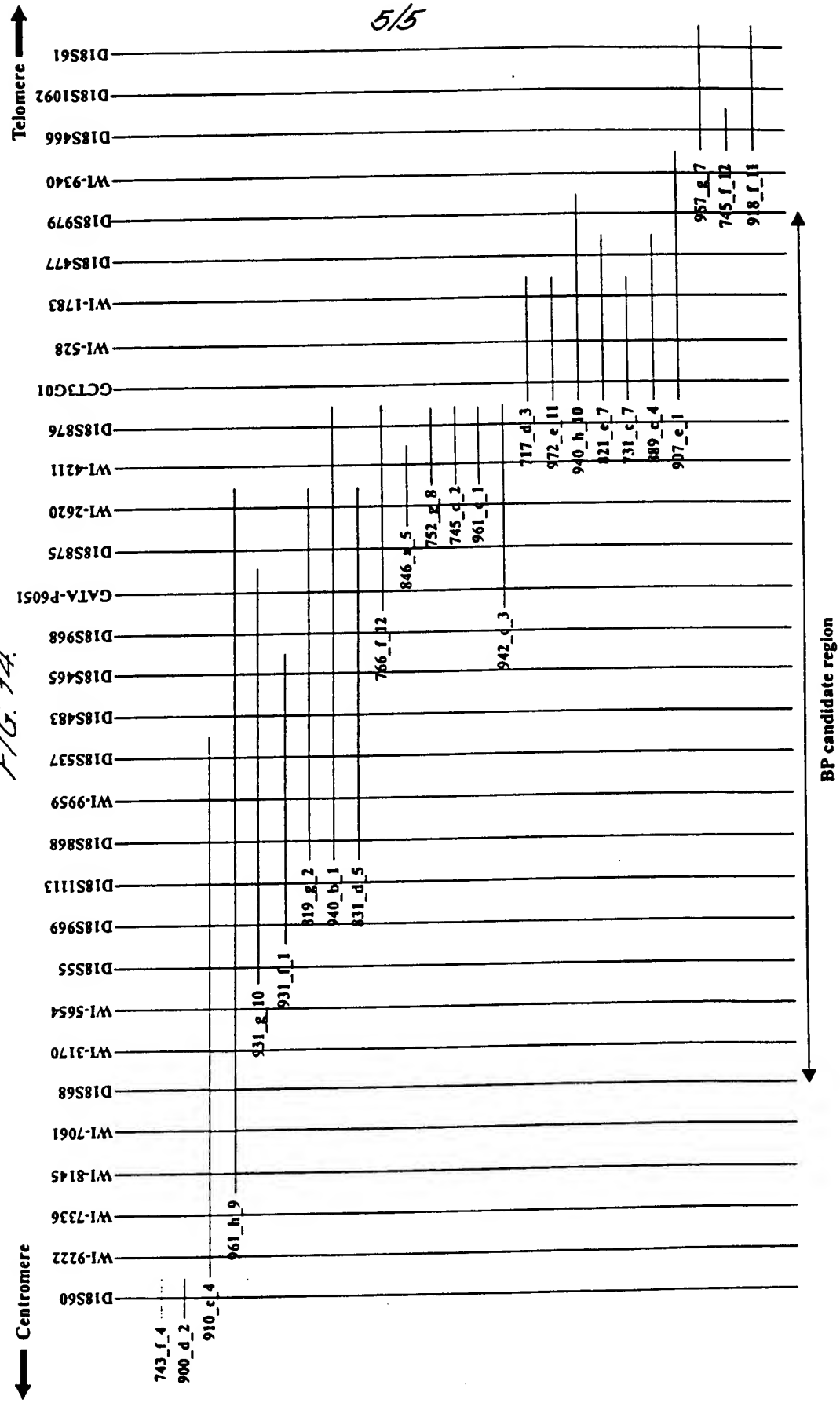
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752_g_8
745_d_2
961_c_1
717_d_3
972_e_11
940_h_10
821_e_7
731_c_7
889_c_4
907_e_1
957_g_7
745_f_12
918_f_11
BP candidate region

FIG. 14.